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RESEARCH PAPER

Association between a lifestyle-based healthy heart score and risk of frailty in older women: a cohort study

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Abstract

Background: Evidence on the comprehensive role of lifestyle in frailty risk is scarce. To assess the association between a lifestyle-based Healthy Heart Score (HHS), which estimates the 20-year risk of cardiovascular disease (CVD), and risk of frailty among older women.
Methods: Prospective cohort study in 121,700 nurses from the USA participating at the Nurses' Health Study. This study included 68,416 women aged ≥60 year with a follow-up from 1990 to 2014. The HHS was computed using the gender-specific beta-coefficients of the nine lifestyle factors, including current smoking, high body mass index, low physical activity, lack of moderate alcohol intake and unhealthy diet. Frailty incidence was assessed every 4 years from 1992 to 2014 as having ≥3 of the following five criteria from the FRAIL scale: fatigue, low strength, reduced aerobic capacity, having ≥5 illnesses and weight loss ≥5%.
Results: During 22 years of follow-up, 11,041 total incident cases of frailty were ascertained. Compared to women in the lowest quintile of the HHS (lowest estimated CVD risk), the multivariable-adjusted hazard ratio of frailty across quintiles was: Q2:1.67 (95% confidence interval 1.53, 1.82); Q3: 2.34 (2.15, 2.53); Q4: 3.54 (3.28, 3.83) and Q5: 5.92 (5.48, 6.38); *P*-trend > 0.001. Results were consistent for each frailty criterion, among participants with 0 frailty criteria at baseline, when using only baseline exposure or in 6-year-, 10-year- and 14-year-exposure lagged analyses, and after excluding participants with diabetes and CVD at baseline.
Conclusions: The HHS, based on a set of modifiable-lifestyle factors, is strongly associated with risk of frailty in older women.

Keywords: cardiovascular disease (CVD) risk prediction, lifestyle, frailty, older adults, Nurses' Health, Older people

Key Points

- Cardiovascular disease (CVD) and frailty share some underlying etiological factors.
- A modifiable-lifestyle CVD prediction tool is strongly associated with the risk of frailty in older women.
- The association remained strong among those without any frailty criteria at baseline, and for each of the frailty criteria.

Introduction

The Healthy Heart Score (HHS), based on nine modifiable health behaviours, has been shown to predict the 20-year risk of cardiovascular disease (CVD) in mid-adulthood [1]. This score has also been associated with the development of clinical CVD risk factors (hypertension, high cholesterol and diabetes) [2] and with total and cause-specific mortality [3]. Establishing if a single index, such as the HHS, is associated with a broad range of health outcomes is paramount because it may help motivate an individual to adopt a set of behaviours to prevent a greater range of chronic disease outcomes. In this regard, an extremely important health outcome in older adults is the frailty syndrome, because its prevalence is expected to increase with population ageing over the next decades, and because of its serious health consequences, including falls, hospitalisation, institutionalisation or death [4].

There is some evidence that CVD and frailty share some underlying etiological factors. Specifically, frailty is more frequent in older adults with endothelial dysfunction [5], biological cardiovascular risk factors [6], or CVD [7]. Also one study using the Framingham cardiovascular risk score showed that men and women with higher score were more likely to become frail over a period of 4 years [8], and a second study demonstrated that reaching old age in ideal cardiovascular health (optimal values of the 7 American Heart Association health metrics) was associated with a reduced risk of frailty [9]. Finally, a combination of behaviours related to CVD, either traditionally healthy behaviours (not smoking, vigorous to moderate physical activity, healthy diet) or emerging healthy behaviours (adequate sleeping duration, not being sedentary and daily social interaction) was associated with lower risk of frailty in older adults [10].

However, no previous study has investigated if a higher HHS is associated with lower risk of frailty in older adults. Given the previous evidence, we hypothesised that a higher HHS will be associated with greater risk of frailty. If observed, promotion of a better adherence the HHS Score could serve to decrease frailty risk in addition to reduced CVD risk. Thus, the HHS could be a useful tool for promoting overall health in the old age. Therefore, our aim is to study the association between the HHS and the risk of frailty in older women in the Nurses' Health Study (NHS).

Methods

Study participants

The NHS is an ongoing prospective cohort that began in 1976 with the enrollment of 121,700 female nurses aged 30–55 years in 11 US states [11]. Participants completed mailed questionnaires to update information on their medical history and health-related behaviours every 2 years [11]. Additionally, participants completed a validated semi-quantitative food frequency questionnaire (FFQ) every 4 years to collect dietary information [12–14]. This FFQ is reasonably valid for measuring habitual food consumption and nutrient intakes compared with multiple dietary records, 24-hour dietary recalls, and biomarkers of diet [15, 16]. In this analysis, we included women aged ≥60 year at baseline with valid dietary information (>500 Kcal/day and < 3,500 Kcal/day) during the follow-up. We excluded participants with missing information on the exposure of interest (the HHS and each of its components) and those identified as frail at baseline (1992) or died before baseline. Women <60 year at baseline and with valid information on diet and lifestyle entered to the analysis when they reached 60 year during the follow-up in subsequent questionnaire cycles. After exclusions, the total analytic sample was 68,416 women. Follow-up was up to 2014 (Figure S1). The Harvard TH Chan School of Public Health and Brigham and Women's Hospital Human Subjects Committee Review Board approved the protocol of the study, and participants provided written informed consent.

Healthy Heart Score

The HHS was based on a 20-year CVD-risk prediction model using the gender-specific coefficients already derived in our cohorts of a set of modifiable behavioural factors: smoking, alcohol intake, body mass index (BMI), physical activity and a diet score that includes five components, namely cereal fibre intake, and consumption of fruits/vegetables, nuts, sugary drinks and red and processed meats. The HHS has been previously derived and validated separately for men (in the Health Professional Follow-Up Study) and women (in the NHS), showing good discrimination, fit and calibration [1]. The final sex-specific β coefficients for the factors that best estimated CVD risk are reported in the Figure S2. A higher HHS indicates higher CVD risk. In addition, as we did for other outcomes such as CVD death or overall mortality [3], age was set as a constant in the prediction model because (i) we were interested in the modifiable components of the HHS, and (ii) age is predictive of all clinical conditions, including frailty. Information about food components in the HHS were retrieved from the FFQ every 4 years. Participants were asked how often on average during the previous year they had consumed each food (with specification of standard portion sizes). Cereal fibre and alcohol intake were calculated by multiplying the nutrient content of each food item (from the Harvard University Food Composition Database) by the frequency of intake, and summed across all food items. We used the residual method to adjust cereal fibre for total energy [17]. We calculated the average of alcohol intake (gram per day), assuming 12.8 g of alcohol in 12 oz of beer, 11.0 g of alcohol in 4 oz of wine and 14.0 g of alcohol in 1.5 oz of liquor. Physical activity was assessed with a validated physical activity questionnaire [18, 19] and we estimated hours per week spent in moderate or vigorous activity (≥3 metabolic equivalent task). Smoking (never, past or current) and BMI (calculated as weight/height^2 were assessed on each biennial self-reported questionnaire [20].

Ascertainment of frailty

We used the FRAIL scale [21], which has previously been used in the NHS [22]. The FRAIL scale comprises five self-reported frailty criteria: fatigue, poor strength (reduced resistance), reduced aerobic capacity, having several illnesses and a significant weight loss during the previous year. In 1992, 1996, 2000, 2004, 2008 and 2012 the NHS participants completed the Medical Outcomes Study Short-Form (SF-36), a 36-item-questionnaire with eight health dimensions, including physical and mental components [23]. From the SF-36, we assessed the first three frailty criteria with the following questions: (i) for fatigue: 'Did you have a lot of energy?,' with replies 'some of the time' or 'none of the time' (in years 1992, 1996 and 2000), and the statement 'I could not get going' in an updated version of the SF-36 (in 2004, 2008, and 2012), with responses 'moderate amount' or 'all of the time'; (ii) for poor strength: 'In a normal day, is your health a limitation to walk up 1 flight of stairs?,' with responses 'yes' or 'a lot'; and (iii) for reduced aerobic capacity: 'In a normal day, is your health a limitation to walk several blocks or several miles?,' with responses 'yes' or 'a lot.' In addition, the illnesses criterion was assessed from the question, 'In the last 2 years, have you had any of these physician-diagnosed illnesses?' We considered that this criterion was met when participants reported ≥5 of the following diseases: cancer, hypertension, type 2 diabetes, angina, myocardial infarction, stroke, congestive heart failure, asthma, chronic obstructive lung disease, arthritis, Parkinson's disease, kidney disease and depression. Finally, the weight loss criterion was defined as a ≥5% decrease in weight reported in two consecutive follow-up cycles. At the end of each follow-up cycle, incident frailty was defined as having ≥3 criteria on the FRAIL scale.

Ascertainment of mortality

Deaths were identified from the state vital statistics records and the National Death Index or reported by families and the postal system. Using these methods, 98% of deaths in the cohort were ascertained. For all deaths, we sought death certificates and, when appropriate, requested permission from the next of kin to review medical records to determine the underlying cause of death, classified according to the International Classification of Diseases, Ninth Revision [24].

Statistical analysis

Women aged ≥60 year contributed person-time from baseline until the occurrence of frailty, death or the end of the study period (1 June 2014), whichever came first. In our primary analysis we used the cumulative average of the HHS from repeated time points before each assessment of frailty to best estimate the long-term exposure and reduce measurement error. We used quintiles of the HHS as the main exposure (Q5, highest estimated CVD risk by the HHS versus Q1, lowest estimated CVD risk (reference)). Cox proportional hazards models were used to calculate age- and multivariable-adjusted hazard ratios (HRs) and 95% confidence interval (CI) of frailty by quintiles of HHS. Multivariable models were adjusted for age, medication use including postmenopausal hormone use, and treatment with aspirin, diuretics, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other antihypertensive medication, statins and other cholesterol-lowering drugs, insulin, and oral hypoglycemic medication (yes or no), and energy intake. Linear trends across quintiles of the HHS were calculated by assigning the median value to each quintiles and modelling as a continuous variable. The sample for the main analysis included only participants with <3 frailty criteria at baseline (non-frail at baseline). Additionally, we examined the association of the HHS with each individual criterion of frailty. We repeated the analysis among those without any frailty criteria at baseline.

Other sensitivity analyses included (i) lagged analyses (6,10, 14 year) to reduce reverse causation or bias due to change in lifestyles resulting from the development of the individual criteria of frailty discarding the first 6, 10 and 14 years of follow-up respectively, (ii) excluding those with diabetes, CVD or cancer at baseline to assess the independence of the study association from the main chronic diseases, (iii) using most recent information on the HHS as exposure, and finally (iv) using only baseline information on the HHS (including those participants that turn 60 year over the follow-up of the analysis). Analyses were performed with SAS software, version 9.4 (SAS Institute Inc.).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results.

Results

Women in the fifth quintile of the HHS (highest estimated CVD risk), tended to have higher BMI, were more likely to have ever smoked, had lower diet quality (lower fruit and vegetable consumption, nuts and cereal fibre and higher consumption of red meat and sugar and sweetened beverages) and were less physically active (Table 1). Total energy intake was similar across quintiles of HHS. Medication use was also higher in the highest versus the lowest quintile of HHS, except for aspirin use, and cholesterol medication that was similar across quintiles, and postmenopausal hormone therapy whose use decreased across quintiles (highest versus the lowest quintile).

During 22 year of follow-up, 11,041 women newly fulfilled the criteria for frailty. In the multivariable-adjusted model, the HHS was strongly associated with the risk of frailty (multivariable HR [95%CI] 5.92 [5.48, 6.38] for Q5 versus Q1, and 1.42 [1.41, 1.44] per 5% increase in the 20-year CVD risk; Table 2), with a strong linear association (P-trend < 0.001). When we evaluated those with none of

Table 1. Age-adjusted baseline characteristics according to quintiles of the Healthy Heart Score among women aged ≥60 year in the Nurses' Health Study ($n = 68,416$)*

	Predictive 20 year CVD risk based on the Healthy Heart Score				
	Quintile 1 (lowest estimated CVD risk)	Quintile 2	Quintile 3	Quintile 4	Quintile 5 (highest estimated CVD risk)
Participants, *n*	12,799	12,980	13,167	13,631	15,839
Healthy Heart Score (20 year risk)	14.1 (2.1)	17.5 (2.2)	19.8 (3.0)	24.1 (4.5)	36.7 (9.7)
Healthy Heart Score components					
Age, year	62.7 (2.3)	62.7 (2.3)	62.6 (2.3)	62.6 (2.2)	62.3 (2.1)
BMI, Kg/m^2	22.2 (2.2)	24.1 (2.4)	26.1 (2.7)	28.8 (3.5)	30.1 (7.0)
Never smoker, %	40	33	29	25	13
Fruits and vegetables, s/day	5.7 (2.5)	5.2 (2.4)	4.9 (2.4)	4.7 (2.4)	4.3 (2.3)
Sugar-sweetened beverages, s/day	0.1 (0.3)	0.2 (0.4)	0.2 (0.4)	0.3 (0.6)	0.4 (0.7)
Red and processed meats, s/day	0.7 (0.6)	0.9 (0.6)	1.1 (0.7)	1.2 (0.8)	1.3 (0.9)
Cereal fibre, g/day	7.4 (4.6)	6.2 ss(3.0)	5.7 (2.8)	5.3 (2.7)	4.9 (2.5)
Nuts, s/day	0.3 (0.5)	0.3 (0.4)	0.3 (0.4)	0.2 (0.4)	0.2 (0.4)
Alcohol intake, g/day	8.0 (9.5)	5.9 (9.0)	4.5 (8.3)	4.0 (8.7)	6.0 (13.0)
Physical activity, MET-h/week	34.2 (32.9)	22.2 (21.5)	17.9 (20.0)	14.9 (17.9)	13.0 (17.5)
Energy intake, Kcal	1755 (443)	1742 (449)	1739 (470)	1756 (487)	1767 (496)
Medication use†, %					
Aspirin	49	47	48	47	47
Postmenopausal hormone therapy	49	46	43	39	34
Diuretics	5	7	9	11	10
β-Blockers	8	10	12	14	13
Calcium channel blockers	6	8	9	11	11
ACE inhibitors	6	7	9	10	11
Other blood pressure medication	5	6	7	9	10
Statins	14	12	13	15	14
Other cholesterol medication	3	3	3	3	3
Insulin	1	1	1	2	3
Oral hypoglycemic drugs	0	1	2	4	5
Number of frailty criteria, %					
0	86	81	75	68	62
1	13	17	21	25	29
2	2	3	4	6	9

*Values are means (SDs) unless otherwise indicated. Data, except age, were directly standardised to the age distribution of the entire cohort. ACE, angiotensin-converting enzyme; BMI, Body Mass Index; ME, metabolic equivalent task. †One or more times per week.

the frailty criteria at baseline (robust participants), the corresponding results were similar (5.48 [5.01, 6.00]; 1.43 [1.41, 1.45]); *P*-trend < 0.05; Table 2). The HHS was significantly associated with higher risk of each of the individual frailty criteria in both age-adjusted models and in multivariable models ($P < 0.05$; Table 3).

Results for 6-, 10-, 14-year lag analyses showed only a slight attenuation across years (multivariable HR [95% CI] of Q5 versus Q1: 6-year lag 4.57 [4.25, 4.91]; 10-year lag 4.32 [4.01, 4.64] and 12-year lag 4.10 [3.79, 4.45]; Supplementary Table S1).

Compared to the cumulative average of estimated HHS over follow-up, when we used the most recent information of the HHS before the development of frailty, again we found an increased risk of frailty when comparing participants in the highest versus the lowest quintile (HR: 5.92; 95% CI: 5.48, 6.38; Supplementary Table S2). In further sensitivity analysis, we excluded individuals with CVD, cancer or diabetes ($n = 9,086$) and the associations remained similar (Supplementary Table S3). In addition, when we used only baseline information for the HHS of women who were ≥60 year at baseline or who turned 60 year during the follow-up (their baseline information), the association, while strong and robust, was slightly attenuated in comparison with the main analysis (HR Q5 versus Q1: 4.19; 95% CI; 3.92, 4.49; Supplementary Table S4).

Finally, each individual component of the HHS was significantly associated with the risk of frailty in the expected direction in the multivariable model with additional adjustment of each individual component (Supplementary Table S5).

Discussion

In this large prospective US cohort of women aged ≥60 year, we found that a higher risk of CVD estimated by the HHS (a tool that includes only modifiable-lifestyle factors) was strongly associated with increased risk of frailty in a dose–response fashion. The association remained strong among those without any frailty criteria at baseline, and for each of the frailty criteria.

Table 2. Hazard ratios (95% confidence intervals) of frailty according to quintiles of the Healthy Heart Score scores among women aged ≥60 year in the Nurses' Health Study (1992–2014)

	Quintile 1 (lowest estimated CVD risk)	Quintile 2	Quintile 3	Quintile 4	Quintile 5 (highest estimated CVD risk)	*P*-trend	Per 5% increase in the HHS
Participants, $n = 68,416$							
Persons-years	201,353	199,830	198,759	196,678	194,419		
Frailty cases (n total = 11,041)	841	1,447	1975	2,869	3,909		
Age-adjusted model	Ref 1.0	1.72 (1.58, 1.88)	2.46 (2.26, 2.66)	3.83 (3.55, 4.14)	6.46 (5.99, 6.96)	<0.001	1.45 (1.43, 1.47)
Multivariable model*	Ref 1.0	1.67 (1.53, 1.82)	2.34 (2.15, 2.53)	3.54 (3.28, 3.83)	5.92 (5.48, 6.38)	<0.001	1.42 (1.41, 1.44)
Robust (0 frailty criteria)							
Participants, $n = 54,754$							
Persons-years	164,683	163,641	162,805	161,484	159,980		
Frailty cases (n total = 7,541)	614	1,021	1,384	1906	2,616		
Age-adjusted model	Ref 1.0	1.66 (1.51, 1.84)	2.33 (2.12, 2.57)	3.45 (3.15, 3.78)	5.96 (5.46, 6.52)	<0.001	1.45 (1.43, 1.47)
Multivariable model*	Ref 1.0	1.62 (1.46, 1.79)	2.22 (2.02, 2.44)	3.20 (2.92, 3.50)	5.48 (5.01, 6.00)	<0.001	1.43 (1.41, 1.45)

*Multivariable model, adjusted for age, energy intake and medication use (aspirin, postmenopausal hormone replacement therapy, diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other blood pressure medication, statins and other cholesterol-lowering drugs, insulin, oral hypoglycemic medication).

Table 3. Association between the Healthy Heart Score (in quintiles, HR and 95% CI) and each frailty criterion among women aged ≥60 year in the Nurses' Health Study (1992–2014)

	Quintile 1 (lowest estimated CVD risk)	Quintile 2	Quintile 3	Quintile 4	Quintile 5 (highest estimated CVD risk)	*P*-trend	Per 5% increase in the HHS
Fatigue: 29,345 cases							
Age-adjusted model	Ref 1.0	1.25 (1.20, 1.29)	1.42 (1.36, 1.47)	1.57 (1.51, 1.63)	1.80 (1.73, 1.86)	<0.001	1.13 (1.12, 1.13)
Multivariable model*	Ref 1.0	1.23 (1.18, 1.28)	1.39 (1.33, 1.44)	1.51 (1.46, 1.57)	1.73 (1.67, 1.80)	<0.001	1.12 (1.11, 1.13)
Low strength: 10,399 cases							
Age-adjusted model	Ref 1.0	1.64 (1.51, 1.77)	2.13 (1.97, 2.30)	2.94 (2.73, 3.17)	4.43 (4.12, 4.78)	<0.001	1.34 (1.33, 1.36)
Multivariable model*	Ref 1.0	1.61 (1.49, 1.75)	2.08 (1.92, 2.24)	2.83 (2.62, 3.05)	4.25 (3.95, 4.57)	<0.001	1.33 (1.31, 1.35)
Reduced aerobic capacity: 21,746 cases							
Age-adjusted model	Ref 1.0	1.57 (1.48, 1.65)	2.04 (1.94, 2.15)	2.83 (2.69, 2.97)	3.81 (3.63, 4.00)	<0.001	1.30 (1.29, 1.31)
Multivariable model*	Ref 1.0	1.54 (1.46, 1.62)	1.98 (1.88, 2.09)	2.70 (2.57, 2.84)	3.62 (3.44, 3.81)	<0.001	1.29 (1.28, 1.30)
≥5 illnesses: 4,196 cases							
Age-adjusted model	Ref 1.0	1.35 (1.19, 1.52)	1.71 (1.52, 1.93)	2.51 (2.25, 2.80)	3.43 (3.08, 3.82)	<0.001	1.30 (1.27, 1.32)
Multivariable model*	Ref 1.0	1.27 (1.12, 1.43)	1.54 (1.37, 1.73)	2.12 (1.90, 2.37)	2.81 (2.52,3.14)	<0.001	1.25 (1.22, 1.27)
Weight loss ≥ 5 kg: 24,033 cases							
Age-adjusted model	Ref 1.0	1.22 (1.17, 1.28)	1.45 (1.38, 1.51)	1.70 (1.63, 1.77)	1.87 (1.80, 1.95)	<0.001	1.14 (1.13, 1.15)
Multivariable model*	Ref 1.0	1.22 (1.17, 1.28)	1.43 (1.37, 1.50)	1.67 (1.60, 1.75)	1.85 (1.77, 1.92)	<0.001	1.13 (1.12, 1.14)

Values are expressed as hazard ratios (95% confidence intervals). *Multivariable model, adjusted for age, energy intake and medication use (aspirin, postmenopausal hormone replacement therapy, diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other blood pressure medication, statins and other cholesterol-lowering drugs, insulin, oral hypoglycemic medication).

The association between the HHS and frailty is robust because it remained strong in several sensitivity analyses. We used cumulative average of the HHS in the main analysis because it reflects long-term health habits and may reduce measurement error over time. However, one concern in this analysis is that changes in health behaviours may result from a health-related diagnosis preceding frailty. By contrast, the lagged analysis allows an evaluation of the latency between the HHS and frailty occurrence, which makes reverse causality unlikely. The 6-, 8- and 10-year-lagged analysis showed a strong association with frailty that was attenuated only slightly over time. In addition, because frailty as well as CVD develops slowly over time, we also used one single baseline exposure that reflected a slightly weaker association likely due to less precise measurement of long-term behaviours. By contrast using the most recent HHS led to similar association with frailty, which might reflect the fact that health habits tend to consolidate with time until a disease diagnosis.

Comparison with previous studies

There is evidence that health behaviours play a major role in the development of frailty. Although most of the studies have only provided evidence of the effect of individual behaviours (diet [22, 25–29], tobacco [30, 31], alcohol consumption [32], BMI [33] or physical activity [34]) on frailty, fewer studies have focused on the overall lifestyle in association with health outcomes, [2, 35] and even fewer studies have used frailty as an outcome and a lifestyle prediction score as exposure [10, 36, 37]. Using an integrated lifestyle approach may translate into stronger associations than examining each individual healthy behaviour, due to additive and synergistic effects.

Our results are in agreement with evidence from observational [10, 37–39] and intervention studies [40–42] that suggest that a multicomponent intervention can be successful in reducing frailty. In the Diabetes Prevention Program Outcome Study early (at about 50 year) lifestyle intervention reduced frailty later in life among participants at high risk of diabetes. Interestingly, the look AHEAD study found that the effect of a lifestyle intensive intervention for weight loss on CVD incidence among individuals with overweight/obesity and diabetes depended on the baseline frailty status, with lower benefit for those with highest frailty scores [42]. Although the study used the Rockwood criteria to define frailty status, and not the FRAIL scale, it supports our findings and the potential use of the HHS to prevent age-related functional decline in addition to primordial prevention of CVD risk factors and CVD. Our study also found strong associations among participants who were not frail and without CVD, cancer and diabetes at baseline, which further supports the potential benefit of targeting individuals for promotion of a healthy lifestyle before the occurrence of chronic diseases and the accumulation of other health deficits during the life course [6]. In this regard in a recent study, Gil-Salcedo *et al.*, found that healthy behaviours at age 50, as well as improvements in behaviours over midlife, were associated with lower risk of frailty later in life [38].

Possible explanations and practical implications

The association between the health behaviours included in the HHS and frailty is biologically plausible. There is evidence that a poor quality diet is associated with increased chronic inflammation and oxidative stress, which play a key pathogenic role in frailty [43, 44]. A poor diet may also contributes to a higher BMI, which is also proinflammatory due to the release of leptin and other cytokines from adipose tissue [45]; moreover, insulin resistance and diabetes resulting from obesity are also important risk factors for frailty [43, 46, 47]. The underlying mechanisms for lower risk of frailty associated with consuming small amounts of alcohol are not entirely clear. There is consistent evidence that alcohol intake is associated with higher levels of high-density lipoprotein cholesterol and adiponectin, lower levels of fibrinogen and improved markers of glucose metabolism, which may reduce frailty risk [39, 43, 46]. Also, alcohol is often consumed socially, and moderate consumption was shown to facilitate social bonding [48], which seems to protect from frailty [49, 50]. Tobacco smoking may increase the risk of frailty due to the detrimental effects of smoking on a wide range of organs and tissues, leading to many chronic diseases that may contribute to frailty [30, 51]. Moreover, inflammation and DNA-methylation could act as a key mediator because cigarette smoke contains several toxic chemicals and has been shown to be associated with increased levels of various inflammatory mediators [52]. Finally, a recent systematic review of observational and intervention studies has concluded that physical activity probably prevents frailty among people aged 65 years and older. The mechanisms likely involved are increased muscle strength and physical performance, but further research is needed on the modality of physical activity or the dose necessary to produce preventive benefits on frailty [34].

Strengths and limitations of the study

Strengths of this study included a large cohort of women, with repeated measures of diet, other lifestyle factors and potential confounders, as well as high rates of follow-up. Additionally, we focused only on a set of modifiable-lifestyle factors that can potentially be changed by behavioural counselling and, thus, reduce frailty risk. However, some limitations need to be acknowledged. Due to the self-reported nature of lifestyle variables, measurement error is inevitable; nonetheless the prospective collection of data makes this error likely non-differential with respect to the outcome, which would underestimate the true association. Also, reverse causation is possible; however, we conducted several sensitivity analyses to reduce this bias. Moreover, generalizability of our results may be limited to women, with a similar high education and socioeconomic status and race. By contrast, the fact that the study cohort is rather homogeneous in those variables may help reduce

confounding; notwithstanding this, and the fact that analyses were adjusted for many potential confounders, we acknowledge that certain residual confounding cannot be rule out. Finally, to ascertain frailty we used the FRAIL scale, which is only one out of a many scales available [53].

Conclusion

The HHS, a CVD-risk prediction tool based on a set of modifiable lifestyles factors, is strongly associated with risk of frailty in older women. Future interventions should consider the integral lifestyle approach to reduce both CVD and frailty risk and promote healthy ageing.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: None.

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