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Nontraditional Cardiovascular Risk Factors in Active Octogenarians Who Develop Cardiovascular Events

Non-traditional risk factors for cardiovascular events in active octogenarians

To the editor:

Cardiovascular disease (CVD) is highly prevalent and contributes to disease burden and mortality in older adults.[1] The American Heart Association concluded that CVD is the leading cause of death in octogenarians, followed by cancer and Alzheimer's disease.[1] Studies questioned the validity of traditional CVD risk factors to predict CVD-related events in older adults.[2,3] Therefore, we explored differences in non-traditional risk factors between octogenarians with *versus* without cardiovascular events across a 4.5-years follow-up.

Methods

The study was approved by the regional Medical Ethical Committee (CMO, region Arnhem-Nijmegen, NL18245.091.07) and conducted in accordance with the Declaration of Helsinki. Subjects were recruited from participants of the Nijmegen Four Days Marches, a (non-competitive) marching event where participants walk 30-40 km/day on four days. Baseline assessments were conducted 1-2 days before the event in July 2016, and included traditional risk factors and non-traditional risk factors (cardiac biomarkers, vascular function, physical performance). Post-exercise cardiac biomarkers were measured after the first walking day. In January/February 2021, a phone interview determined occurrence of major cardiac adverse events (stroke, transient ischemic attack, myocardial infarction, heart failure or revascularization) during follow-up. Participants who passed away were excluded, as

the cause of death could not be determined. Framingham Risk Scores for CVD and coronary heart disease, and the Dutch version of the Systematic Coronary Risk Evaluation were calculated.[4–6] Cardiac troponin I was measured with a contemporary troponin I assay (upper reference limit: 40 ng/L), B-type natriuretic peptide (BNP) with a high sensitive assay. For the Short Physical Performance Battery (SPPB), higher scores indicate better functioning.[7] Vascular function was examined using the carotid artery reactivity test.[8] Differences between octogenarians with *versus* without incident major cardiac adverse events during follow-up were assessed in R-studio, version 3.6.2.

Results

Fifty-seven participants (median age 83 years, mean BMI 25 kg/m^2, 28% female) were included for analysis, with 12 (21%) reporting at least one major cardiac adverse event. Regarding traditional risk factors (Table 1), only systolic blood pressure and the Systematic Coronary Risk Evaluation were significantly different in those with incident major cardiac adverse events (P<0.05). Regarding non-traditional markers, BNP and cardiac troponin I levels were significantly increased after 30-40km of walking (both P<0.001). Baseline cardiac troponin I, post-exercise cardiac troponin I, and post-exercise BNP were higher in those with incident major cardiac adverse events, while physical performance (SPPB) was lower (Table 1, all P<0.05).

Discussion

Our findings reinforce that traditional CVD risk factors have limited clinical value in octogenarians, as most traditional risk factors did not differ between octogenarians with *versus* without incident major cardiac adverse events. However, we did find

higher systolic blood pressure in the group with events. Different weighing of systolic blood pressure within the Systematic Coronary Risk Evaluation *versus* Framingham Risk Scores may explain why we found a difference between groups for the former, but not the latter. Possibly, the Systematic Coronary Risk Evaluation holds higher value than the Framingham Risk Scores in octogenarians. Nonetheless, a potential reason for limited value of traditional risk factors is that octogenarians who have survived event-free *with* specific risk factors may be less susceptible to those specific risk factors.[2,9] Alternatively, physiological changes during aging causing the cardiovascular system to adjust, might moderate the impact of traditional risk factors.[2,9] Hence, alternative markers that reflect CVD risk accumulated throughout life might be more suitable for risk prediction in older adults.

Our study provides first evidence that post-exercise levels of cardiac biomarkers could be a novel marker of potential relevance in older adults. To our knowledge, this is the first study to evaluate post-exercise BNP markers for CVD risk in general. However, post-exercise levels were assessed after a 30-40 km walk, which is not feasible for clinical risk assessment. Future studies should focus on post-exercise cardiac markers after shorter bouts of controlled exercise or exercise testing. Markers of vascular health did not differ between groups. Possibly, markers that better reflect long-term exposure to cardiovascular risk factors (e.g. coronary calcification[10]) are needed, as the vascular outcomes used in our study can be susceptible to relatively rapid changes. We did not see differences in physical activity levels or handgrip strength between groups, which may have been a result of the active nature of our study population. This also limits the generalizability of our results to a more inactive/frail population. Nonetheless, differences were found for

the SPPB, which combines mobility, balance and strength, rather than assessing one domain only. Such combination seems more susceptible to detect differences between groups than individual measures of physical performance.

Our work highlights the potential importance of (post-exercise) cardiac markers and the SPPB, as a simple measure of physical performance, to assess cardiovascular risk in octogenarians. An advantage of the SPPB over cardiac biomarkers is that it is easily administrable and inexpensive.

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Tables

Table 1. Traditional and non-traditional risk factors and incident of MACE: group differences

	No MACE (N=45)	n	MACE (N=12)	n	P-value
Traditional risk factors					
Systolic BP (mmHg)	148 [139; 154]	44	158 [151; 161]	10	**0.034**
Diastolic BP (mmHg)	83 ± 11	44	87 ± 9	10	0.41
Total cholesterol (mmol/l)	5.3 [4.6; 5.8]	44	5.2 [4.1; 6.1]	12	0.70
LDL (mmol/l)	2.9 [2.6; 3.4]	43	2.8 [2.4; 3.4]	12	0.75
HDL (mmol/l)	1.7 (0.5)	44	1.6 (0.6)	12	0.39
Triglycerides (mmol/l)	1.2 [0.9; 1.8]	44	1.4 [1.0; 1.7]	12	0.72
History of CVD (yes)	8 (17.8%)	45	1 (8.3%)	12	0.67
Diabetes (yes)	3 (6.7%)	45	1 (8.3%)	12	1.00
Framingham CVD score	15.6 ± 2.1	43	16.6 ± 1.8	10	0.17
Framingham CHD score	8.0 [7.0; 8.5]	43	8.0 [7.0; 9.8]	10	0.89
SCORE-NL CVD mortality risk (%)	5.0 [4.0; 6.0]	42	7.0 [5.3; 8.8]	10	**0.030**
SCORE-NL CVD mortality + events risk (%)	16.0 [14.0; 19.0]	42	22.5 [15.8; 25.8]	10	**0.040**
Non-traditional risk factors					
cTnI (ng/l)	0.0 [0.0; 3.5]	43	6.0 [1.8; 18.5]	12	**0.003**
cTnI > URL	1 (2.3%)	43	0 (0.0%)	12	1.00
cTnI post-exercise (ng/l)	21.0 [6.5; 47.0]	43	47.0 [34.0; 101.0]	11	**0.044**
cTnI post-exercise > URL	12 (27.9%)	43	7 (63.6%)	11	**0.038**
BNP (ng/l)	25.0 [16.2; 46.7]	43	36.3 [26.9, 77.5]	12	0.13
BNP post-exercise (ng/l)	42.0 [19.6; 71.9]	43	75.2 [58.9; 91.7]	11	**0.020**
Carotid artery reactivity (%)	2.0 ± 2.8	45	1.1 ± 4.0	12	0.36
SPPB score	11.0 [10.0; 12.0]	44	10.0 [9.0; 10.0]	11	**0.011**
Relative handgrip strength (kg/kg/m^2)	1.3 ± 0.3	43	1.2 ± 0.2	12	0.09*
Total physical activity (MET-h/week)	82.3 [58.4; 150.9]	45	70.3 [45.1; 111.6]	12	0.36

MACE, major adverse cardiovascular event; BP, blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; CVD, cardiovascular disease; CHD, coronary heart disease; SCORE-NL, Dutch version of the Systematic Coronary Risk Evaluation. cTnI, cardiac troponin I; URL, upper reference limit; BNP, B-type natriuretic peptide; SPPB, Short Physical Performance Battery (range 0-12). Normally distributed data are presented as mean ± SD and analyzed with independent samples t-test, unless otherwise indicated; non-normal data as median [25th percentile; 75th percentile], analyzed with Mann-Whitney U test. Categorical data are presented as number (%), analyzed with Fischer exact test. *Welch t-test.

Age, sex, and BMI were not different between groups and there were no current smokers among participants.

APPENDIX

Methods

Study design

In July 2016, a group of 83 physically active older (≥80 years) subjects were recruited. Participants provided written informed consent for baseline assessments and were asked for consent to participate in the follow-up. Seven participants did not give consent for follow-up and were excluded resultantly. The study was approved by the regional Medical Ethical Committee (CMO, region Arnhem-Nijmegen, NL18245.091.07) and conducted in accordance with the Declaration of Helsinki. Subjects were recruited from participants of the Nijmegen Four Days Marches, which is a (non-competitive) marching event where participants walk 30 to 40 km per day on four consecutive days. Baseline assessment of participant characteristics and risk factors took place one or two days before the start of the Four Day Marches. Post-exercise cardiac troponin I and BNP were assessed after the first walking day. In January and February 2021, a telephone interview was conducted with the participants to document the occurrence of major cardiac adverse events during the 4.5-year follow-up period. Participants who passed away during this period were excluded as information about major cardiac adverse events was not available and cause of death was unknown.

Traditional risk factors and risk scores. Body weight (Seca 888 Scale; Seca, Hamburg, Germany) and height were measured and used to calculate BMI (kg/m^2). At baseline, participants filled in an online questionnaire to assess age, sex, smoking status, history of cardiovascular disease (transient ischemic attack, stroke,

myocardial infarction, heart failure, medication use) and diabetes. Blood pressure was measured after a minimum of 5 minutes rest in supine position (Omron M6, Omron healthcare Co., Ltd., Kyoto, Japan).

To measure biomarkers, venous blood was drawn from an antecubital vein. All blood samples were taken in a non-fasted state. Drawn blood was centrifuged and serum stored at -80°C until analysis. Total cholesterol (enzymatic, colorimetric method, mmol/l), high-density lipoprotein (homogeneous enzymatic, colorimetric test, mmol/l), low-density lipoprotein (calculated, mmol/l), and triglycerides (enzymatic, colorimetric method, mmol/l) were analyzed.

The Framingham Risk Score for cardiovascular disease was calculated as described by D'Agostino *et al.*[1] The Framingham Risk Score for coronary heart disease was calculated as described by Wilson *et al.* [2] The Dutch version of the Systematic Coronary Risk Evaluation was calculated, which gives a risk indication for 10-year cardiovascular mortality and for cardiovascular morbidity and mortality.[3,4]

Cardiac biomarkers. Cardiac troponin I (contemporary troponin I assay, ADVIA Centaur TnI-Ultra; Siemens Healthcare Diagnostics, The Hague, The Netherlands; upper reference limit (URL): 40 ng/L; coefficient of variation: 8.8% at the URL and 10% at 30 ng/L; detection limit (LOD): 6 ng/L but assay does report values below the LOD) and BNP (high sensitive BNP assay, Centaur BNP, Siemens Healthcare Diagnostics, The Hague, The Netherlands; coefficient of variation: 20% at 2.5 ng/L, 4.7% at 30 ng/L, and 2.3% at 1500 ng/L; detection limit: 2 ng/L) were analyzed at baseline and post-exercise. For post-exercise samples, blood was drawn approximately 10 minutes after completion of the first walking day.

Vascular health. We examined carotid artery reactivity (CAR) as a direct measure of vascular health, which has demonstrated independent prognostic value for future CVD-related events in patients with peripheral arterial disease and correlates with coronary artery function.[5,6] To determine CAR, the left common carotid artery (CCA) diameter was assessed by ultrasound (Terason T300, Terason, Burlington, Massachusetts, USA) during a one-minute baseline recording and a three-minute Cold Pressor Test (CPT). Ultrasound assessments were made with a linear probe in B-mode. During the CPT, the hand of the participant was immersed in cold water (≤ 4°C), up to the wrist. Analysis of the ultrasound recordings was done with edge-detection and wall-tracking software and an independent assessor reviewed the analyses. The diameter during the one-minute baseline recording was averaged to obtain the baseline diameter. During the CPT, the CCA diameter was averaged in 10-second intervals. In response to the sympathetic activation induced by the CPT, the CCA can dilate, constrict or not show a change. Directionality (dilation/constriction) of the response was defined based on a positive or negative difference between the mean diameter during CPT and the mean baseline diameter. The peak dilation or constriction diameter of the 10 second intervals was then used to calculate CAR%:

CAR%= ((peak diameter−baseline diameter)/ baseline diameter) *100%.

Previously reported coefficients of variation for CAR% reproducibility were 2.6% for within-day assessments (1 hour) and 2.8% for between-day (24 hour) assessments.[6]

Physical performance. Handgrip strength (kg) of the dominant hand was assessed with a handheld dynamometer (Jamar, Jackson, MI, USA) in seated position, with a 90° angle of the elbow. Three consecutive assessments were performed and the

maximum handgrip strength was used for analysis. Physical functioning was assessed with the Short Physical Performance Battery (SPPB).[7] The total SPPB score (0-12) was calculated by summing the scores for the individual components: balance (0-4 points), gait speed (0-4 points), and ability to rise from a chair (0-4 points). Higher scores indicate better physical functioning. Physical activity levels were assessed online with the Short Questionnaire to Assess Health enhancing physical activity (SQUASH). This questionnaire has been validated, including for use in older adults.[8,9] Metabolic Equivalent of Task (MET) values were assigned using the Compendium of Physical Activities.[10] Resultantly, physical activity levels were expressed in MET-hours/week.

Follow-up

Twelve participants passed away during the follow-up period and were excluded. Resultantly, 64 were contacted for follow-up by phone in the beginning of 2021 (January/February), of whom six withdrew and one could not be reached. During the phone interview, participants were asked to indicate if they had ever experienced a major cardiac adverse event. In this study, the following events were included as major cardiac adverse event*:* stroke, transient ischemic attack, myocardial infarction, heart failure or revascularization. In case of a confirmative answer, they were asked to indicate the year and month of the diagnosis. Events that occurred before July 2016 were defined as history of CVD. Events that occurred after July 2016 were defined as incident major cardiac adverse events.

Statistical analysis

Continuous variables were depicted as mean ± standard deviation (SD) when normally distributed and median [25th percentile-75th percentile] when not normally distributed. Normality was assessed with the Shapiro-Wilk test and inspected via Q-Q plots and histograms. Categorical variables were reported as number (%). Differences in baseline characteristics between octogenarians with *versus* without incident major cardiac adverse events were assessed using the independent t-test for normally distributed continuous variables, Mann-Whitney U test for non-normal data, and Chi-Square test for categorical data. In case of a normal distribution but unequal variances, the Welch t-test was applied. In case of an expected cell count below five, the Fischer exact test was applied. To assess pre- and post-exercise differences in BNP and cardiac troponin I, the non-parametric Sign test was applied. The alpha was set at 0.05. Analyses were performed in R-studio version 3.6.2.[11] The R-studio tableone package was used for descriptives and analysis of baseline differences.[12]

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