Data and Methods Supplement

Supplemental Methods for Covariates in Exercise Intolerance Analysis

As noted in Table 1, the analysis examining the association of NT-proBNP with exercise intolerance adjusted for demographic factors, smoking (pack-years), diet quality, physical activity and performance measures known to impact exercise capacity.

Moderate or vigorous physical activity was reported as minutes per week on the National Health and Nutrition Survey Physical Activity Questionnaire[1] and diet quality as the score on the Healthy Eating Index, out of 100, with the average score of the US population being 59.[2,3]

Performance measures included the following: chronotropic incompetence[4] or blunted blood pressure (BP) response[5] defined as survivors who achieved < 80% of age- and sex-predicted heart rate reserve (≤62% if taking β blockers or calcium channel blockers)[6] or had < 20 mmHg systolic BP rise during CPET, forced expiratory volume in 1 second (FEV_1) measured using prebronchodilator spirometry and impairment was defined as FEV_1 < 80% predicted for race and sex,[7] seated, relative isokinetic quadriceps strength (Newton-meters per kilogram) converted to age- and sex-specific z scores based on values from community controls (Biodex System 4; Biodex Medical Systems, Shirley, NY)[8,9], and the modified total neuropathy scale (MTNS) to evaluate peripheral sensorimotor function with scores ≥ 5 (of 24) used to define impairment.[10] Resting heart rate, respirations, and BP were measured after 5 minutes of quiet sitting before exercise testing. Heart rate and BP were also measured during the test, at peak exercise, and 2 and 5 minutes into recovery.

Table S1. Abnormal NT-proBNP cut-points defined by 97.5th percentile limit of normal by age and sex (from the Framingham Heart Study)

Age Group (Years)	NT-proBNP (pg/ml) 97.5th Quantile reference limit	
	Men	Women
20-24	42.5	111.0
25-29	48.5	122.1
30-34	55.3	134.3
35-39	63.0	147.6
40-44	71.8	162.4
45-49	81.9	178.5
50-54	93.3	196.3
55-59	106.4	215.9

Table S2. Grading of cardiovascular risk factors and other chronic health conditions by modified common terminology criteria for adverse events (CTCAE) v4.03

Condition	Grading Source	Grading Rubric	
Left ventricular systolic dysfunction (Includes cardiomyopathy)	**Modified** CTCAE v4.03 Investigations: Ejection fraction decreased (grades 2&3) Left ventricular systolic dysfunction (grade 4)	1: Not applicable 2: Resting EF < 50-40%; 10 - 19% absolute drop from baseline 3: Resting EF 39-20%; >20% absolute drop from baseline; medication indicated or initiated 4: Resting EF<20%; refractory or poorly controlled heart failure due to drop in ejection fraction; on medical management; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated 5: Death	
Dyslipidemia			
High total cholesterol	**Modified** CTCAE v4.03 Investigations: Cholesterol high	1: >200 mg/dL - 300 mg/dL 2: >300 - 400 mg/dL; treatment with one lipid lowering agent 3: >400 - 500 mg/dL; treatment with >=2 lipid lowering agent 4: >500 mg/dL 5: Not applicable	
Hypertriglyceridemia	**Modified** CTCAE v4.03 Metabolism and Nutrition Disorders: Hypertriglyceridemia	1: 150 mg/dL - 300 mg/dL 2: >300 mg/dL - 500 mg/dL; treatment with one lipid lowering agent 3: >500 mg/dL - 1000 mg/dL; treatment with >=2 lipid lowering agents 4: >1000 mg/dL; life-threatening consequences 5: Death	
Hypertension	**Modified** CTCAE v4.03 Vascular Disorders: Hypertension	1: Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg) 2: Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated or initiated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated or initiated 3: Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated or initiated 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated 5: Death	
Diabetes mellitus	**Modified** CTCAE v4.03 Metabolism and nutrition disorders: Glucose intolerance	1: Asymptomatic; clinical or diagnostic observations only; pharmacologic intervention not indicated or initiated (e.g. dietary modification) 2: Symptomatic; oral agent indicated or initiated 3: Severe symptoms; insulin indicated or initiated 4: Life threatening consequences, urgent intervention indicated or initiated 5: Death	
Overweight/Obesity	Criteria per Centers for Disease Control and Prevention guidelines	For age >= 20 years 1: Not applicable 2: BMI 25 - 29.9 kg/m2 3: BMI 30 - 39.9 kg/m2	For age 2 - <20 years 1: Not applicable 2: BMI >= 85th%ile <95th%ile 3: BMI > 95th%ile

		4: BMI >=40 kg/m2 5: Not applicable	4: Not applicable 5: Not applicable
Underweight	Criteria per Centers for Disease Control and Prevention guidelines	For age >= 20 years 1: Not applicable 2: BMI < 18.5 kg/m2 3: Not applicable 4: Not applicable 5: Not applicable	For age 2 -< 20 years 1: Not applicable 2: BMI < 5th%ile 3: Not applicable 4: Not applicable 5: Not applicable
Coronary artery disease (Includes myocardial infarction)	**Modified** CTCAE v4.03 Cardiac Disorders: Myocardial infarction	1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated 2: Mild symptoms and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes 3: Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction (Q waves) 4: Life-threatening consequences; hemodynamically unstable (CABG or angioplasty) 5: Death	
Cerebrovascular accident (Includes: lacunes, hemorrhagic stroke, Ischemic stroke)	CTCAEv4.03 Nervous system disorders: Stroke	1: Asymptomatic or mild neurologic deficit; radiographic findings only 2: Moderate neurologic deficit 3: Severe neurologic deficit 4: Life-threatening consequences; urgent intervention indicated 5: Death	
Vascular disease (Stenosis/occlusion of vessel other than coronary or cerebral vessels, e.g., carotid, subclavian)	CTCAE v4.03 Vascular Disorders Other, specify	1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL 4: Life-threatening consequences; urgent intervention indicated 5: Death	

Table S3. Characteristics of survivors with diagnosed grade 3 or 4 cardiomyopathy prior to the study date by medical management status.

Population	**Current treatment N=37**		**No current treatment N=12**		
	N	%	N	%	P
Cardiomyopathy Grade					
Grade 3	29	78.4	11	91.7	0.302
Grade 4	8	21.6	1	8.3	
Treatment					
Beta-blocker alone	7	18.9			
ACEi/ARB alone	3	8.1			
Loop diuretic alone	1	2.7			
ACEi + beta blocker	12	32.4			
ACEi + loop diuretic	2	5.4			
All three classes	12	32.4			
Ejection Fraction, %*					
≥53	13	40.6	5	41.7	1.000
40 - <53	16	50.0	6	50.0	
<40	3	9.4	1	8.3	
NT-proBNP					
Overall**					
Normal	12	32.4	4	33.3	1.000
Abnormal	25	67.6	8	66.7	
Value, pg/ml					
<50	7	18.9	1	8.3	0.266
50-125	6	16.2	5	41.7	
126-450	11	29.7	4	33.3	
>450	13	35.1	2	16.7	

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

*Ejection Fraction at the time of the current visit (biomarker analysis).

**NT-proBNP based on age- and sex- specific 97.5th quantile regression reference limits reported by Fradley et al. using the Framingham cohort.

Table S4. Characteristics of childhood cancer survivors exposed and not exposed to anthracycline chemotherapy and/or chest-directed radiotherapy

	All Survivors N=1213	**Exposed Survivors N=786**	**Non-exposed Survivors N=427**
	N (%)	**N (%)**	**N (%)**
Age at diagnosis, years. (median – IQR)	8.7 (3.7-14.3)	10.0 (4.2-14.7)	7.1 (3.1-12.9)
Age at evaluation, years (median – IQR)	35.5 (29.8-42.5)	35.9 (30.2-42.7)	34.3 (28.3-42.3)
Time since diagnosis, years (median – IQR)	26.4 (19.9-33.8)	26.3 (20.4-33.1)	27.1 (18.7-35.1)
Sex			
Male	623 (51.4)	419 (53.3)	204 (47.8)
Female	590 (48.6)	367 (46.7)	223 (52.2)
Race/ethnicity			
Non-Hispanic White	1016 (83.7)	669 (85.2)	347 (81.3)
Non-Hispanic Black	168 (13.9)	98 (12.5)	70 (16.4)
Hispanic	11 (0.9)	8 (1.0)	3 (0.7)
Other	18 (1.5)	10 (1.3)	7 (1.6)
Health habits (median - IQR)			
Smoking (pack years)	0.0 (0.0-1.8)	0.0 (0.0-2.5)	0.0 (0.0-0.7)
Weekly minutes of MVPA	140.0 (0.0-420.6)	128.5 (0.0-427.2)	153.4 (0.0-415.8)
Healthy Eating Index	58.4 (49.4-67.4)	58.2 (49.0-67.7)	58.6 (50.9-66.5)
Insurance status			
Yes	973 (80.2)	626 (79.6)	347 (81.3)
No	240 (19.8)	160 (20.4)	80 (18.7)
Primary Cancer Diagnosis			
Acute lymphoblastic leukemia	257 (21.2)	151 (19.2)	106 (24.8)
Acute myeloid leukemia	38 (3.1)	37 (4.7)	1 (0.2)
Other leukemia	11 (0.9)	1 (0.1)	10 (2.3)
Hodgkin lymphoma	238 (19.6)	224 (28.5)	14 (3.3)
Non-Hodgkin lymphoma	58 (4.8)	49 (6.2)	9 (2.1)
CNS tumor	177 (14.6)	63 (8.0)	114 (26.7)
Wilms tumor	91 (7.5)	68 (8.7)	23 (5.4)
Retinoblastoma	45 (3.7)	4 (0.5)	41 (9.6)
Soft tissue sarcoma	64 (5.3)	35 (4.5)	29 (6.8)
Neuroblastoma	59 (4.9)	40 (5.1)	19 (4.4)
Osteosarcoma	60 (5.0)	55 (7.0)	5 (1.2)
Ewing sarcoma	50 (4.1)	49 (6.2)	1 (0.2)
Other	65 (5.4)	10 (1.3)	55 (12.9)
Cardiotoxic Therapy Exposures			
Anthracycline Only		366 (46.6)	
Chest RT Only		174 (22.1)	
Chest RT + Anthracyclines		246 (31.3)	
Anthracycline Exposure			
Dose (median - IQR), mg/m^2		204 (152.1-341.6)	
None	601 (49.6)	174 (22.1)	427 (100.0)
1-200 mg/m^2	272 (22.4)	272 (34.6)	
201-350 mg/m^2	196 (16.2)	196 (24.9)	
>350 mg/m^2	144 (11.9)	144 (18.3)	
Chest-directed RT maxTD (Gy)			
None	793 (65.4)	366 (46.6)	427 (100.0)
1-19.9	66 (5.4)	66 (8.4)	

20-29.9	207 (17.1)	207 (26.3)	
≥30	147 (12.1)	147 (18.7)	
Cardiovascular Risk Factors**			
Diabetes Mellitus	120 (9.9)	78 (9.9)	42 (9.8)
Hypertension	346 (28.5)	218 (27.7)	128 (30.0)
Dyslipidemia	179 (14.8)	115 (14.6)	64 (15.0)
BMI, kg/m^2 (median – IQR)***	27.1 (23.5-32.5)	27.0 (23.3–32.2)	27.4 (23.7–33.1)
<18.5	50 (4.1)	37 (4.7)	13 (3.0)
18.5-24.9	354 (29.2)	230 (29.3)	124 (29.0)
25-29.9	389 (32.1)	256 (32.6)	133 (31.2)
≥30	420 (34.6)	263 (33.5)	157 (36.8)
Coronary Artery Disease,*****			
No	1129 (93.1)	714 (90.8)	415 (97.2)
Grade 2	2 (0.2)	2 (0.3)	0 (0.0)
Grade 3	61 (5.0)	52 (6.6)	9 (2.1)
Grade 4	18 (1.7)	18 (2.3)	3 (0.7)
Previous cardiomyopathy§			
No	1109 (91.4)	688 (87.5)	421 (98.6)
Grade 2	55 (4.5)	52 (6.6)	3 (0.7)
Grade 3	40 (3.3)	38 (4.8)	2 (0.5)
Grade 4	9 (0.7)	8 (1.0)	1 (0.2)

MVPA: Moderate or vigorous physical activity; IQR: Interquartile range; RT: Radiation therapy; maxTD: maximum target dose

*Percentages for individual characteristics calculated on total number of participants on whom information was available

**CTCAE grade ≥2 at the time of the evaluation or previously diagnosed

***See Table S2 for CTCAE grading

§ CTCAE grade ≥2 prior to the current evaluation

Table S5. Distribution of cardiac biomarkers among participants exposed and not exposed to cardiotoxic therapy

Population		**Cardiac Troponin-T N=1213**	**NT-proBNP N=1213**		
	N Overall	N abnormal (%)	N abnormal (%)	Median [IQR]	P
Overall	1213	5 (0.4)	273 (22.5)	41.0 [20.0, 84.0]	
Gender					
Female	590	1 (0.2)	114 (19.3)	60.0 [30.0, 121.0]	<0.0001
Male	623	4 (0.6)	159 (25.5)	29.0 [15.0, 62.0]	
Exposure status					
Unexposed Survivors	427	0 (0.0)	32 (7.5)	28.0 [14.0, 57.0]	<0.0001
Exposed Survivors	786	5 (0.6)	241 (30.7)	53.0 [26.0, 110.0]	
Age at assessment in years					
18-20	34	0 (0.0)	3 (8.8)	30.0 [15.0, 42.0]	<0.0001
21-30	353	0 (0.0)	78 (22.1)	34.0 [16.0, 72.0]	
31-40	460	3 (0.7)	101 (22.0)	41.0 [21.0, 82.0]	
41-50	292	2 (0.7)	68 (23.3)	51.0 [24.0, 107.0]	
51+	74	0 (0.0)	23 (31.1)	64.0 [32.0, 186.0]	
Survival time in years					
10-15	139	0 (0.0)	25 (18.0)	32.0 [17.0, 65.0]	<0.0001
16-20	231	1 (0.4)	44 (19.1)	33.0 [17.0, 74.0]	
21-25	220	0 (0.0)	48 (21.8)	42.0 [20.0, 78.5]	
26-30	206	1 (0.5)	56 (27.2)	39.5 [21.0, 86.0]	
31+	417	3 (0.7)	100 (24.0)	51.0 [23.0, 118.0]	
Anthracycline cumulative dose, mg/m^2					
1-200 mg/m^2	272	1 (0.4)	54 (19.9)	44.0 [22.0, 76.0]	<0.0001
201-350 mg/m^2	196	1 (0.5)	65 (33.2)	63.0 [26.0, 122.0]	
>350 mg/m^2	144	1 (0.7)	55 (38.2)	69.5 [31.0, 152.5]	
Chest directed RT dose, Gy					
1-19.9 Gy	66	0 (0.0)	20 (30.3)	41.0 [22.0, 81.0]	0.04
20-29.9 Gy	207	0 (0.0)	52 (25.1)	53.0 [27.0, 94.0]	
≥30 Gy	147	2 (1.4)	72 (49.0)	78.0 [32.0, 212.0]	
Male					
Unexposed survivors	204	0 (0.0)	17 (8.3)	17.0 [9.0, 33.0]	<0.0001
Exposed survivors	419	4 (1.0)	142 (33.9)	36.0 [19.0, 76.0]	
Female					
Unexposed survivors	223	0 (0.0)	15 (6.7)	39.0 [23.0, 78.0]	<0.0001
Exposed survivors	367	1 (0.3)	99 (27.0)	74.0 [39.0, 155.0]	
Male - exposed					
Anthracycline only	190	2 (1.1)	56 (29.5)	32.0 [18.0, 68.0]	0.09
Chest RT Only	110	2 (1.8)	41 (37.3)	42.0 [19.0, 82.0]	
Anthracycline + chest RT	119	0 (0.0)	45 (37.8)	42.0 [24.0, 84.0]	
Female - exposed					
Anthracycline only	176	1 (0.6)	41 (23.3)	68.0 [38.5, 131.0]	0.02
Chest RT only	64	0 (0.0)	26 (40.6)	75.0 [37.0, 149.0]	
Anthracycline + chest RT	127	0 (0.0)	32 (25.2)	122.0 [48.0, 209.0]	
Cardiac event¥					
Cardiomyopathy					
None	1064	3 (0.3)	200 (18.8)	38.0 [19.0,77.0]	<0.0001

Grade 2	89	0 (0.0)	32 (36.0)	58.0 [30.0, 150.0]	
Grade 3	51	1 (0.1)	34 (66.7)	163.0 [62.0, 508.0]	
Grade 4	9	1 (0.1)	7 (77.8)	250.0 [151.0, 664.0]	
Coronary artery disease					
None	1129	4 (0.3)	229 (20.3)	40.0 [20.0, 80.0]	<0.0001
Grade 2	2	0 (0.0)	2 (100.0)	196.0 [186.0, 206.0]	
Grade 3	61	0 (0.0)	30 (49.2)	74.0 [35.0, 190.0]	
Grade 4	21	1 (0.1)	12 (57.1)	88.0 [61.0, 398.0]	

RT: radiation therapy.

*Percentages for abnormal are calculated on total number of participants within each group on whom information was available and abnormal values were defined as troponin-T >0.01 ng/mL and NT-proBNP based on age- and sex- specific 97.5th quantile regression reference limits reported by Fradley et al. using the Framingham Heart Study cohort.

** The percentage in N (% abnormal) is the percent of abnormality in each stratum (row).

*** P values are for comparisons of value distribution using Wilcox test.

¥CTCAE grade at the time of the evaluation or previously diagnosed.

Table S6. Multivariable associations between treatment exposures, traditional cardiovascular risk factors and abnormal NT-proBNP in adult survivors of childhood cancer

			Treatment Exposures Model		**Cardiovascular Risk Factor Model**
	N	Abnormal NT-proBNP, N (%)	RR (95% CI)	P for trend	RR (95% CI)
Sex					
Male	623	159 (25.5)	**1.28 (1.05-1.57)**		**1.29 (1.05-1.59)**
Female	590	114 (19.3)	1.0		1.0
Race/Ethnicity					
Non-Hispanic White	1016	237 (23.3)	1.18 (0.88-1.58)		**1.41 (1.05-1.90)**
Other	197	36 (18.3)	1.0		1.0
Age at diagnosis, years					
<5	392	87 (22.2)	**1.56 (1.14-2.14)**		**1.46 (1.07-2.00)**
5-9.9	269	62 (23.1)	1.26 (0.92-1.73)		1.26 (0.92-1.71)
10-14.9	293	73 (24.9)	1.21 (0.89-1.65)		1.26 (0.93-1.70)
15-20.9	259	51 (19.7)	1.0		1.0
Current age, years					
18-30	387	81 (20.9)	1.0		1.0
31-40	460	101 (22.0)	0.98 (0.76-1.27)		1.05 (0.82-1.36)
>40	366	91 (24.9)	1.10 (0.84-1.42)		1.04 (0.78-1.38)
Anthracycline dose (mg/m2)					
0	601	99 (16.5)	1.0	<0.0001	--
1-200	272	54 (19.9)	**1.39 (1.01-1.91)**		--
201-350	196	65 (33.2)	**2.28 (1.74-2.99)**		--
>350	144	55 (38.2)	**2.99 (2.27-3.95)**		--
Chest-directed RT maxTD dose (Gy)					--
0	793	129 (16.3)	1.0	<0.0001	--
1-19.9	66	20 (30.3)	**1.62 (1.07-2.46)**		--
20-29.9	207	52 (25.1)	**1.68 (1.23-2.30)**		--
≥30	147	72 (49.0)	**3.66 (2.89-4.64)**		--
Cardiovascular Risk Factors*					
Diabetes mellitus*					
No	1093	247 (22.6)	--		1.0
Yes	120	26 (21.7)	--		1.04 (0.73-1.41)
Hypertension*					
No	867	188 (21.7)	--		1.0
Yes	346	85 (24.6)	--		1.06 (0.82-1.36)
Dyslipidemia*					
No	1034	229 (22.5)	--		1.0
Yes	179	44 (24.6)	--		1.02 (0.76-1.36)
BMI (kg/m^2)					
<18.5	50	25 (50.0)	--		**1.43 (1.02-2.00)**

18.5-24.9	354	103 (29.1)	--		1.0
25-29.9	389	76 (19.5)	--		**0.61 (0.48-0.78)**
≥30	420	69 (16.4)	--		**0.57 (0.44-0.75)**
Cardiomyopathy *					
No	1064	200 (18.8)	--		1.0
Grade 2	89	32 (36.0)	--		**1.41 (1.02-1.94)**
Grade 3	51	34 (66.7)	--		**2.59 (1.93-3.47)**
Grade 4	9	7 (77.8)	--		**3.05 (1.94-4.80)**
Coronary Artery Disease *					
No	1129	229 (20.3)			**1.0**
Grade 2 or 3	63	32 (50.8)	--		**1.54 (1.13-2.09)**
Grade 4	21	12 (57.1)	--		1.03 (0.71-1.48)

RR: Relative Risk; CI: Confidence interval; RT: radiation therapy; maxTD: maximum target dose
Analyses modeled the RR of abnormal NT-proBNP adjusting for age at diagnosis, attained age, race, sex and all other covariates in the column.
P-value for trend with increasing dose of cardiotoxic therapy (anthracycline/Chest RT)
*CTCAE grade ≥2 at the time of the evaluation or previously diagnosed.

Table S7. Alternative multivariable associations between treatment exposures and abnormal NT-proBNP in adult survivors of childhood cancer by a combination of dose and cardiotoxic agent exposure

Characteristic			**Treatment Exposures Model**
	N	Abnormal NT-proBNP, N (%)	RR (95% CI)
Sex			
Male	623	159 (25.5)	**1.28 (1.05-1.57)**
Female	590	114 (19.3)	1.0
Race/Ethnicity			
Non-Hispanic White	1016	237 (23.3)	1.22 (0.90-1.64)
Other	197	36 (18.3)	1.0
Age at diagnosis, years			
<5	392	87 (22.2)	**1.63 (1.19-2.22)**
5-9.9	269	62 (23.1)	1.36 (0.99-1.86)
10-14.9	293	73 (24.9)	1.23 (0.90-1.67)
15-20.9	259	51 (19.7)	1.0
Current age, years			
18-30	387	81 (20.9)	1.0
31-40	460	101 (22.0)	0.92 (0.71-1.19)
>40	366	91 (24.9)	1.09 (0.84-1.41)
Exposure Risk			
None	427	32 (7.5)	1.0
Single agent low-dose	151	26 (17.2)	0.47 (0.29-0.76)
Both agents low-dose	22	7 (31.8)	**2.06 (1.02-4.17)**
Single agent high-dose	532	172 (32.3)	**2.09 (1.42-3.06)**
Both agents high-dose	81	36 (44.4)	**3.18 (2.04-4.94)**

RR: Relative Risk; CI: Confidence interval; RT: radiation therapy; maxTD: maximum target dose
Exposure risk was categorized as none (no exposure to either anthracycline chemotherapy or chest RT), single agent low-dose (exposure to either 1-200 mg/m^2 anthracycline OR 1-19.9 Gy chest RT), both agents low-dose (exposure to both 1-200 mg/m^2 anthracycline AND 1-19.9 Gy chest RT), single agent high-dose (exposure to either ≥200 mg/m^2 anthracycline OR ≥20 Gy chest RT, could have received low dose or no exposure to other agent) and both agents high-dose (exposure to both ≥200 mg/m^2 anthracycline AND ≥20 Gy chest RT).

Table S8. Sensitivity, specifitiy and predictive values of abnormal NT-proBNP to identify new reduced LVEF (<53%), abnormal GLS or diastolic dysfunction among survivors previously undiagnosed with cardiomyopathy

	N* (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All Survivors					
LVEF < 53%	171 (16.4)	0.23 (0.17-0.29)	0.82 (0.80-0.85)	0.20 (0.15-0.26)	0.85 (0.82-0.87)
Abnormal GLS	425 (39.8)	0.22 (0.18-0.26)	0.83 (0.80-0.86)	0.47 (0.40-0.54)	0.62 (0.59-0.65)
Diastolic dysfunction	222 (22.1)	0.26 (0.20-0.32)	0.84 (0.81-0.86)	0.31 (0.24-0.38)	0.80 (0.77-0.83)
Survivors exposed to cardiotoxic therapy					
LVEF < 53%	120 (18.3)	0.29 (0.21-0.37)	0.75 (0.72-0.79)	0.21 (0.15-0.27)	0.83 (0.79-0.86)
Abnormal GLS	290 (43.3)	0.30 (0.25-0.35)	0.77 (0.73-0.81)	0.50 (0.43-0.57)	0.59 (0.55-0.63)
Diastolic dysfunction	160 (25.4)	0.31 (0.24-0.39)	0.76 (0.72-0.80)	0.31 (0.24-0.39)	0.76 (0.72-0.80)

This analysis excludes those survivors diagnosed with grade 3 or 4 cardiomyopathy prior to this study.
*N indicates the number of individuals with the outcome of interest (LVEF <53%, abnormal GLS, Diastolic dysfunction).
Note: A 95% CI including 0.5 indicates no significant difference from chance.
LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; PPV: positive predictive value; NPV: negative predictive value

Table S9. CTCAE grade of majore cardiac events among exposed survivors with normal LVEF (≥53%) at baseline

Outcome	Grade 2-4 Events N = 74	Grade 2 Events N=53	Grade 3 Events, N=12	Grade 4 Events, N=9
Myocardial Infarction	11	3	2	6
Cardiomyopathy	52	44	8	0
Vascular Disease	8	6	0	2
Stroke	3	0	2	1

Of note, three survivors expierenced multiple events during follow-up: one with cardiomyopathy and vascular disease, one with myocardial infarction and cardiomyopathy, one with cardiomyopathy, myocardial infarction and vascular disease.

Figure S1. FLOW diagram of study population

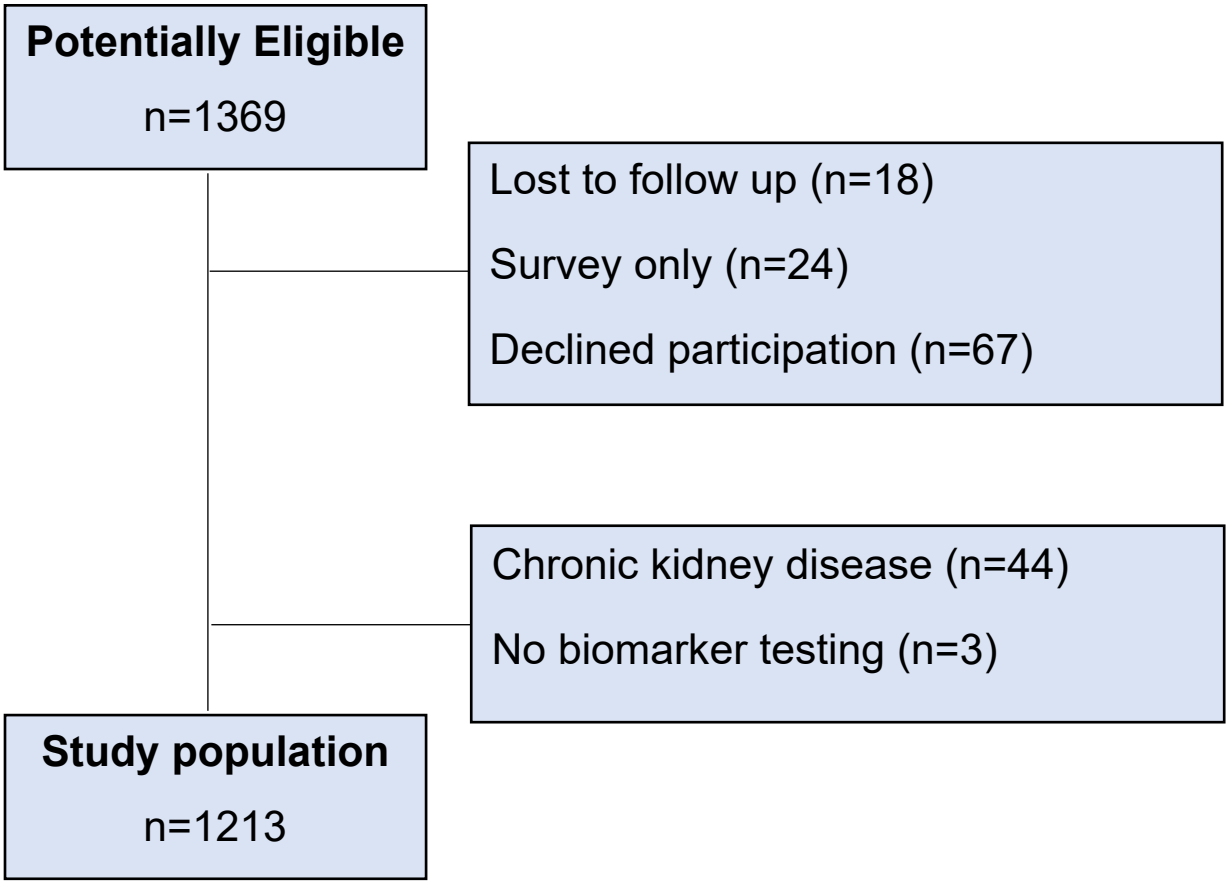
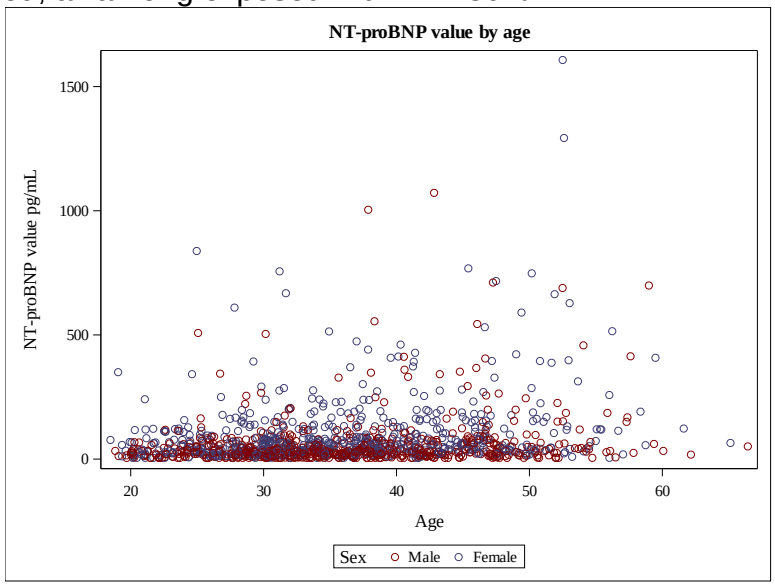
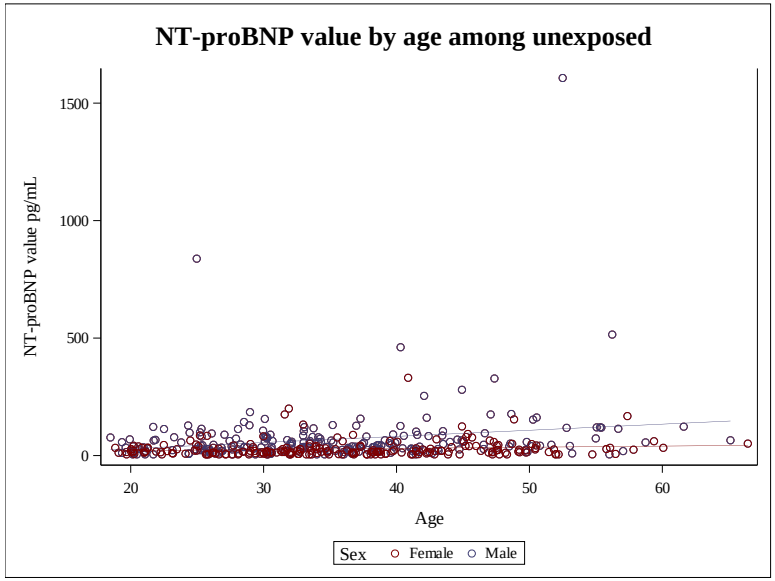


Figure S2. Scatterplots demonstrating the association between NT-proBNP values and a) age, d) ejection fraction (%), g) global longitudinal strain (GLS) z-score, and j) E/e' ratio for diastolic function among b) e) h) k) unexposed and c) f) i) l) exposed. Exposed and unexposed plots include regression lines. Three survivors with NT-proBNP >2000 pg/mL were excluded, all among exposed with EF <50%.

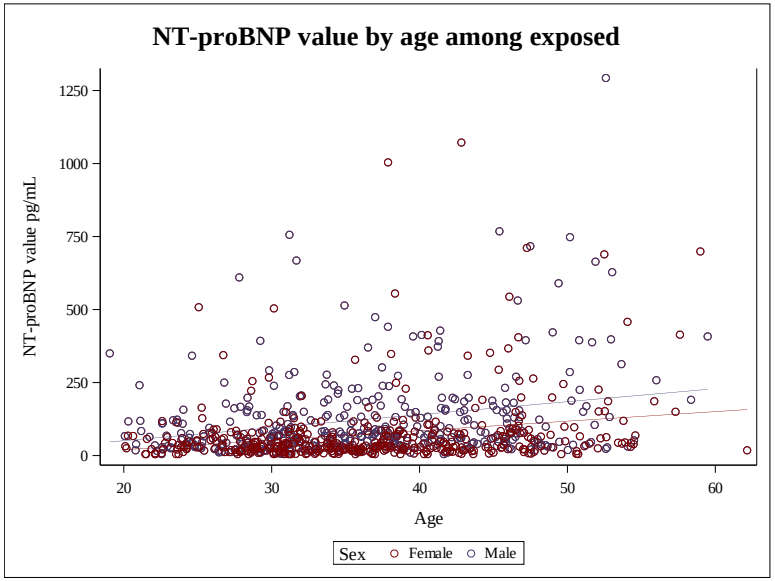
a)



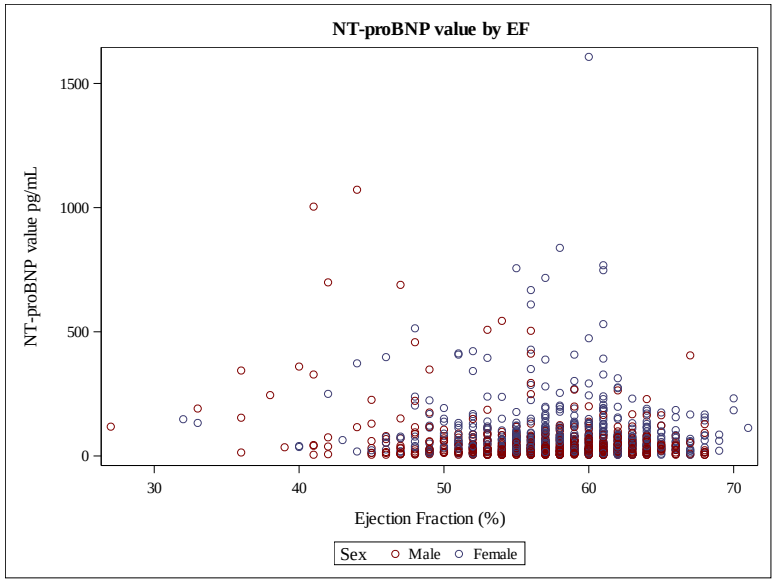
b)



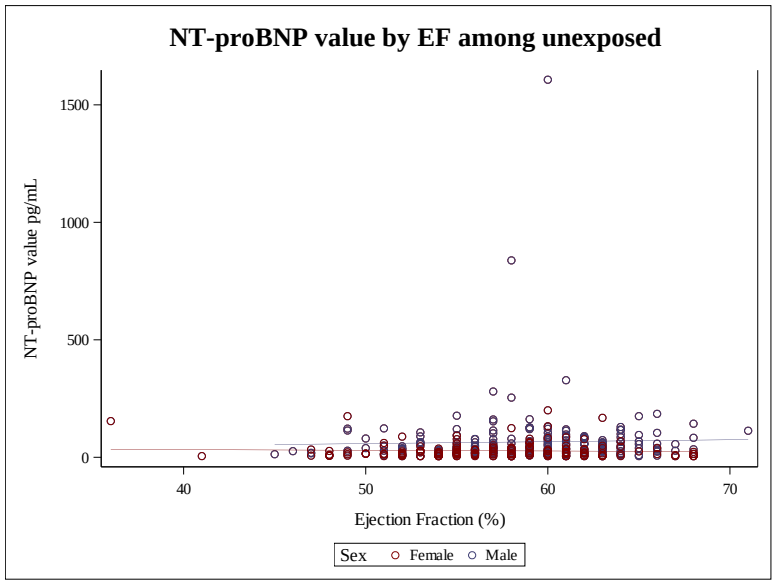
c)



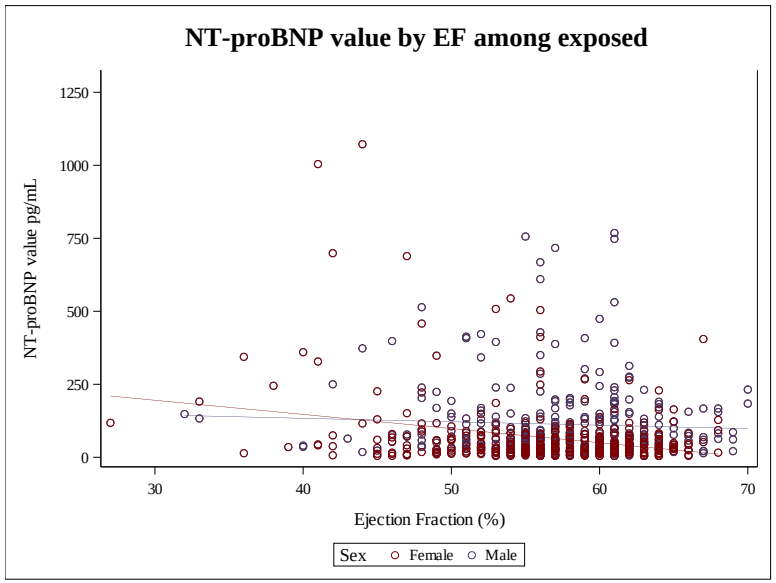
d)


NT-proBNP value by EF
NT-proBNP value pg/mL
1500
1000
500
0
30
40
50
60
70
Ejection Fraction (%)
Sex
Male
Female

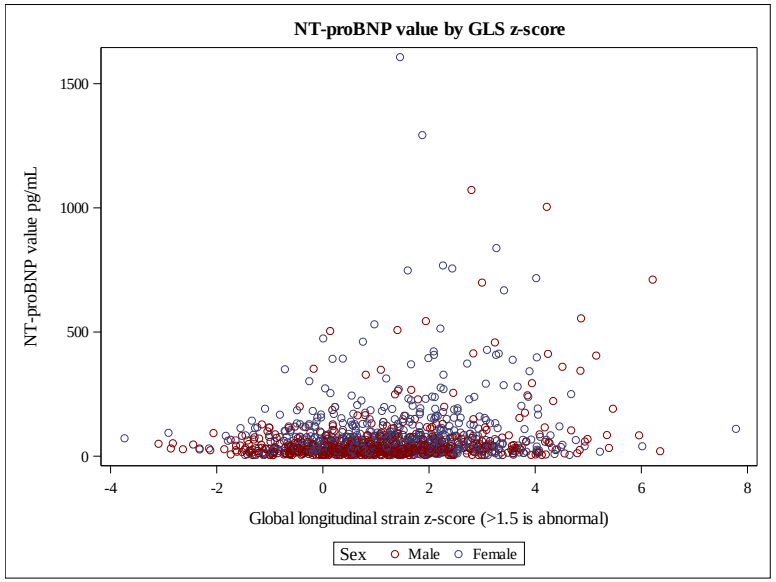
e)


NT-proBNP value by EF among unexposed
NT-proBNP value pg/mL
1500
1000
500
0
40
50
60
70
Ejection Fraction (%)
Sex
Female
Male

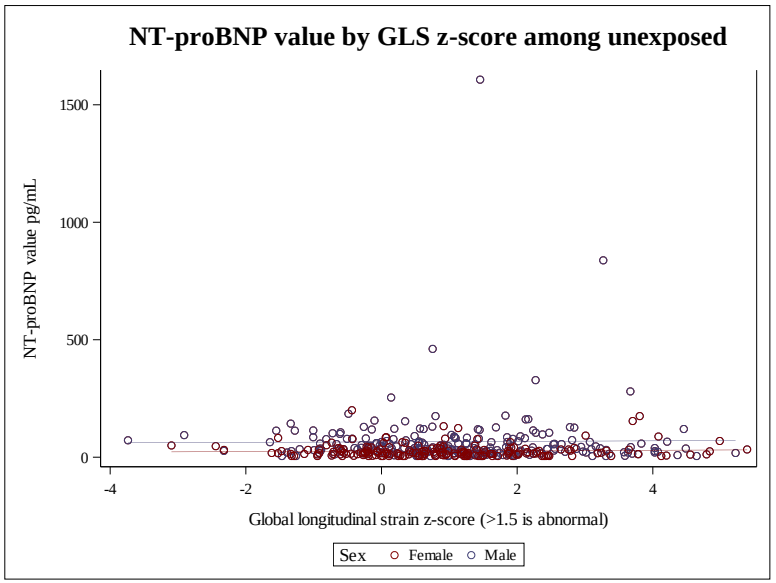
f)


NT-proBNP value by EF among exposed
NT-proBNP value pg/mL
1250
1000
750
500
250
0
30
40
50
60
70
Ejection Fraction (%)
Sex
Female
Male

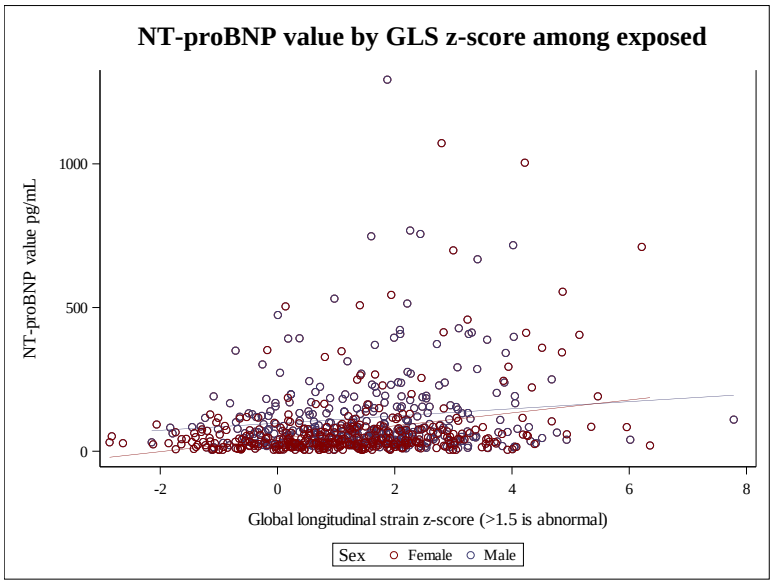
g)


NT-proBNP value by GLS z-score
NT-proBNP value pg/mL
1500
1000
500
0
-4
-2
0
2
4
6
8
Global longitudinal strain z-score (>1.5 is abnormal)
Sex
Male
Female

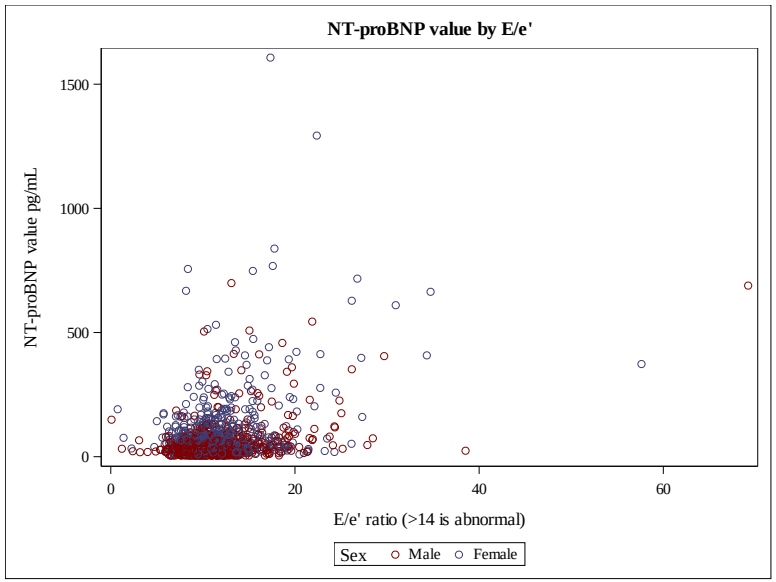
h)


NT-proBNP value by GLS z-score among unexposed
NT-proBNP value pg/mL
1500
1000
500
0
-4
-2
0
2
4
Global longitudinal strain z-score (>1.5 is abnormal)
Sex
Female
Male

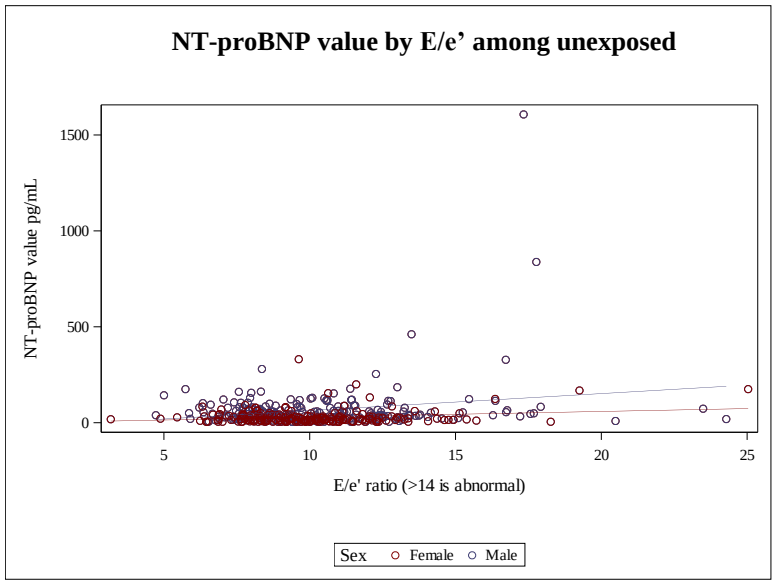
i)


NT-proBNP value by GLS z-score among exposed
NT-proBNP value pg/mL
1000
500
0
-2
0
2
4
6
8
Global longitudinal strain z-score (>1.5 is abnormal)
Sex
Female
Male

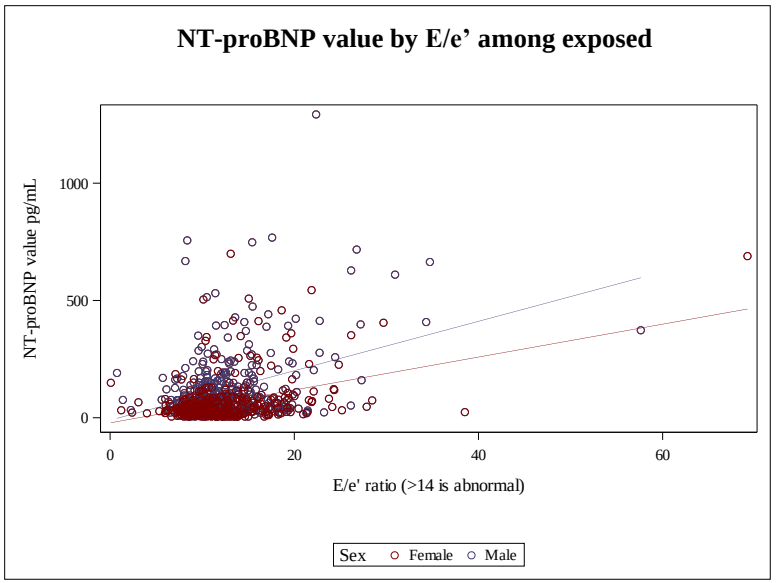
j)


NT-proBNP value by E/e'
NT-proBNP value pg/mL
1500
1000
500
0
0
20
40
60
E/e' ratio (>14 is abnormal)
Sex
Male
Female

k)


NT-proBNP value by E/e' among unexposed
NT-proBNP value pg/mL
1500
1000
500
0
5
10
15
20
25
E/e' ratio (>14 is abnormal)
Sex
Female
Male

l)


NT-proBNP value by E/e' among exposed
NT-proBNP value pg/mL
1000
500
0
0
20
40
60
E/e' ratio (>14 is abnormal)
Sex
Female
Male

References

1. US Department of Health and Human Services: National Health and Nutrition Examination Survey. 2007-2008 Data Documentation, Codebook, and Frequencies. Physical Activity (PAQ_E). 2009. https://wwwn.cdc.gov/Nchs/Nhanes/2007-2008/PAQ_E.htm#Component_Description.
2. Dietary Guidelines for Americans 2015-2020. 8th ed. http://health.gov/dietaryguidelines/2015/guidelines/.
3. Krebs-Smith SM, Pannucci TE, Subar AF, et al. Update of the Healthy Eating Index: HEI-2015. *J Acad Nutr Diet.* 2018;118(9):1591-1602.
4. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation.* 2011;123(9):1010-1020.
5. Schultz MG, La Gerche A, Sharman JE. Blood Pressure Response to Exercise and Cardiovascular Disease. *Curr Hypertens Rep.* 2017;19(11):89.
6. Khan MN, Pothier CE, Lauer MS. Chronotropic incompetence as a predictor of death among patients with normal electrograms taking beta blockers (metoprolol or atenolol). *Am J Cardiol.* 2005;96(9):1328-1333.
7. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319-338.
8. Feiring DC, Ellenbecker TS, Derscheid GL. Test-retest reliability of the biodex isokinetic dynamometer. *J Orthop Sports Phys Ther.* 1990;11(7):298-300.
9. Ness KK, Plana JC, Joshi VM, et al. Exercise intolerance, mortality, and organ system impairment in adult survivors of childhood cancer. *J Clin Oncol.* 2020;38(1):29-42.
10. Wampler M, Miaskowki C, Byl N, Rugo H, KS T. The modified total neuropathy score: A clinically feasible and valid measure of taxane-induced peripheral neuropathy in women with breast cancer. *J Support Oncol.* 2006;4:W9-W16.