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Impact of acquired comorbidities on all-cause mortality rates among older breast cancer survivors

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Abstract

Background—Breast cancer survivors with higher numbers of comorbidities at the time of primary treatment suffer higher rates of all-cause mortality than comparatively healthier survivors. The effect of time-varying comorbidity status on mortality in breast cancer survivors, however, has not been well investigated.

Objective—We examined longitudinal comorbidity in a cohort of women treated for primary breast cancer to determine whether accounting for comorbidities acquired after baseline assessment influenced the hazard ratio of all-cause mortality compared with an analysis using only baseline comorbidity.

Methods—Cox proportional hazards adjusted for age, race/ethnicity, and exercise habits were modeled using (1) only a baseline Charlson index; (2) four Charlson index values collected longitudinally and entered as time-varying covariates, with missing values addressed by carrying forward the prior observation; and (3) the four longitudinal Charlson scores entered as time-varying covariates, with missing values multiply imputed.

Results—The three modeling strategies yielded similar results; Model 1 HR: 1.4 per unit increase in Charlson index, 95% CI: 1.2, 1.7; Model 2 HR: 1.3, 95% CI: 1.1, 1.5 and Model 3 HR: 1.4, 95% CI: 1.2, 1.6.

Conclusions—Our findings indicate that a unit increase in the Charlson comorbidity index raises the hazard rate for all-cause mortality by approximately 1.4-fold in older women treated for primary breast cancer. The conclusion is essentially the same whether accounting only for baseline comorbidity or accounting for acquired comorbidity over a median follow-up period of 85 months.

Keywords

aged; chronic disease; breast neoplasms; comorbidity; mortality

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Introduction

Breast cancer is primarily a disease of older women, who frequently have other diseases as well.^{1, 2} When present, these diseases may affect breast cancer treatment choices and adherence to treatment regimens,²⁻⁸ which would directly affect breast cancer mortality and therefore affect overall mortality. Medical attention focused on the treatment of breast cancer may also detract from definitive care of comorbid disease, and therefore increase all-cause mortality rates in breast cancer patients. Evidence for this phenomenon has been reported for serious diseases other than breast cancer.^{9, 10}

Recent years have witnessed a surge of investigations into the role comorbidity plays in the treatment and care of older cancer patients. Past studies have examined the effect of comorbid conditions on cause-specific and all-cause mortality rates, showing that older breast cancer survivors with a greater burden of comorbidity suffer from higher rates of all-cause mortality than those who are healthier.^{4, 6, 8, 11, 12} To date, no study of this association has accounted for changes in comorbidity beyond the period of initial cancer treatment. We have expanded upon previous research by accounting for acquired comorbidity and examining its effect on all-cause mortality in a cohort of older women diagnosed with early stage breast cancer.

Methods

Study population

We conducted our study within an ongoing prospective cohort of older women diagnosed with early-stage breast cancer. The enrollment criteria and data collection procedures for this cohort have been described in detail elsewhere.¹³ Briefly, women aged 65 years or older diagnosed with early stage breast cancer (stage I with tumor diameter ≥ 1 cm, stage II or stage IIIa) between 1996 and 1999 at one of 61 hospitals in Rhode Island, North Carolina, Minnesota, or Los Angeles were identified through tumor registries and hospital pathology reports. Women whose physicians gave contact permission were invited to participate (**n=1,621**). Additional entry criteria included: (1) no prior history of primary breast cancer, (2) no simultaneously diagnosed primary tumor at another anatomic site, (3) English-speaking or with an available translator, and (4) competent for interview with satisfactory hearing or with an available proxy respondent. Women who were not enrolled within 5 months of the date of their breast cancer surgery were excluded. Of the 1,621 women whose physicians gave contact permission, 865 consented to participate in the study and were subsequently enrolled. All participants returned a signed consent form approved by local institutional review boards.

Participants were interviewed by telephone at 3, 6, and 15 months—and annually thereafter until 87 months—following primary tumor treatment. These interviews collected data on patient demographics, lifestyle, primary tumor and treatment characteristics, cancer recurrence, and comorbid conditions.

Definition of analytic variables

The 3-month interview served as the baseline time point for all subjects, and we restricted the sample to those who successfully completed a baseline interview (n=689). We calculated the number of person-days of follow-up for each individual by extracting the number of days between the date of baseline interview and either the date of death or the date of last completed interview. Of the 689 subjects, 4.1% did not have recorded interview dates but had indicator variables for having completed an interview at each follow-up month. For these subjects, person-days were estimated by multiplying the number of months between surgery and last follow-up by 30.5 days. Eighty-seven subjects were lost to follow-up between the baseline and month 75 interviews; a further 203 were lost to follow-up after the month 75 interview.

Age at time of primary treatment was divided into three categories for descriptive purposes (65-69, 70-79 and >79 years), but was modeled as a continuous variable. Race/ethnicity was self-reported as either Caucasian, African-American, Hispanic, Asian/Pacific Islander, Native American or Other. Regular exercise was defined in the interview question as “physical activity for at least one-half hour a day at least three times per week, with physical fitness being the main purpose of the activity,” exclusive of any exercises prescribed by a subject’s physician or physical therapist. We asked about exercise habits at the 6, 15, 27, 39, 51 and 87 month interviews.

We collected comorbidity data from participants at the 3, 27, 51 and 75 month interviews. We calculated the Charlson index of comorbidity¹⁴ using a method adapted to interview data instead of medical record abstractions.¹⁵ Briefly, we constructed a Charlson score for each subject at each time point by assigning specified weights to 15 contributing health conditions if present at the time of interview. We translated the sum of the accrued weights into the ordinal Charlson index, which ranges from 0 (no comorbidity) to 3 (serious comorbidity). Once a subject reported a health condition it was assumed to persist for the remainder of a subject’s follow-up time. Therefore, a given subject’s Charlson index could either remain static or increase, but could not decrease over their follow-up time. A description of the ordinal Charlson index is given in Table 1.

The outcome for our study was death from any cause, ascertained by vital status queries of the National Death Index (NDI), the Social Security Administration (SSA), the death index of the Centers for Medicare and Medicaid Services (CMS), or by proxy interview response. We ascertained cause of death through regular queries of the National Death Index.

Selection of candidate confounders

We used a directed acyclic graph (DAG) to identify a sufficient set of confounders for analytic control. A DAG encodes hypothesized relations between variables, which can aid in identifying confounders of a given exposure-disease association. Confounders in a DAG are variables along a causal path with arrows pointing into both the exposure and disease (see Greenland et al.¹⁶ for a more complete definition). Figure 1 depicts the hypothesized relationships among the variables that influence comorbidity and all-cause mortality. Using the back-door test described by Greenland et al.,¹⁶ control for age, exercise habits and race/ethnicity were minimally sufficient to address confounding of the association between comorbidity and all-cause mortality, presuming the causal diagram faithfully depicts the causal relations among the variables. In our causal graph, tumor and treatment characteristics appear on the causal pathway between comorbidity and all-cause mortality, making their control inappropriate. To do so would attenuate a portion of the total effect of comorbidity on all-cause mortality, leading to a biased measure of association.

Multiple imputation of missing data

By design, all subjects had a baseline Charlson index. A considerable fraction of subjects (33%) had one or more missing values among their post-baseline Charlson index values, and 76% of subjects were missing one or more values among the six longitudinal exercise variables. To assess and correct for this loss to follow-up, we used a multiple imputation procedure to populate the missing data fields. A qualitative analysis of the data revealed non-monotone patterns of missing values. That is, a missing value for either the Charlson index or exercise status at one time point did not always portend missing values at all future time points. Because of this non-monotonicity, we were limited to using the Markov Chain Monte-Carlo (MCMC) imputation method. The MCMC method imputes continuous values for missing observations by drawing a specified number of fair random samples from a distribution characterized by the known values. Multiple imputation yields estimates of association that incorporate uncertainty

about the imputed values into the variance of a parameter estimate, thus widening confidence intervals.¹⁷ Five imputations were performed for each subject using a single Markov chain and a non-informative prior distribution for the means and covariances of the missing Charlson and exercise data. Because the Charlson index is an ordinal measure, we constrained the range of imputed values between 0 and 3 and rounded to the nearest integer. The imputed dichotomous exercise variables were treated in an analogous manner.

To evaluate the performance of the multiple imputation procedure we selected a random sample of 20 subjects from those with complete Charlson data over the follow-up period (n=462), re-coded the subset's Charlson index values as missing, and imputed these values as described above. We compared the five imputed values at each follow-up point with the corresponding observed values and found that, overall, the imputed values matched the observed values 67% of the time. If the observed Charlson value was zero, the imputation matched 73% of the time, compared to a 56% match rate if the observed value was not equal to zero.

Statistical analysis

We tabulated the number of subjects, cases of death, and person-days for the entire cohort based on socio-demographic, therapeutic and comorbidity characteristics (Table 2). We modeled Cox proportional hazards to examine the effect of comorbidity on all-cause mortality when (1) only baseline Charlson index was modeled, (2) the Charlson index was entered as a time-varying covariate, with missing values in the longitudinal scores addressed by carrying forward the last known observation, and (3) Charlson index was entered as a time-varying covariate, using imputed scores in place of the missing values. For the last of these procedures, five separate Cox models were obtained, one for each of the five imputations, and the results were combined to yield a single parameter estimate and standard error, accounting for the within- and between-imputation variability.¹⁸ All models were additionally adjusted for age (continuous), race/ethnicity (non-Caucasian vs. Caucasian), and time-varying exercise habits (coded as a yes or no response to the regular exercise interview question). Models 1 and 2 were restricted to subjects who had non-missing baseline exercise status (n=612), and missing values for longitudinal exercise habits were addressed by carrying forward the last known value. Imputed exercise status was used in Model 3.

The proportional hazards assumption for the Charlson index was verified for all three models by including a term for the interaction between Charlson index and the logarithm of person-days. The multiple imputation and statistical analyses were performed using SAS version 9 (SAS Institute, Cary, NC).

Results

Six hundred eighty-nine subjects met the eligibility criteria and were included in the analysis. The total follow-up time was 3,927 person-years, with a median individual follow-up time of 85 months. Table 2 displays the baseline characteristics of the analytic cohort. The majority of women in our study were Caucasian (95%), with a median age at enrollment of 73 years (range: 65 to 96 years). Most women (93%) began the study with a Charlson index of either 0 or 1, and 59% exercised regularly at baseline. Almost all of the participants (97%) had stage I or II breast cancer at diagnosis, and about half were treated with mastectomy. Of those who opted for breast-conserving surgery, only 66% received radiation therapy (RT).

Figure 2 shows the distribution of longitudinal Charlson index values before and after multiple imputation. Nearly all imputed Charlson index values were either 0 or 1, with little change in the proportion of moderate to severe comorbidity when combined with the measured values. The combined measured and imputed values demonstrate a trend toward more comorbidity over time, as expected.

Compared to the observed exercise values, the imputed values consistently showed a higher proportion of regular exercisers at each time point, but both sets showed an overall downward trend in the proportion of regular exercisers over time (data not shown).

Results from the three Cox models are shown in Table 3. Time-interaction terms for the Charlson index were non-significant in each of the three models ($P>0.3$ for all), thus verifying proportionality of hazards. The time-interaction terms were excluded from the final models. Each model result shows the relative increase in the hazard rate of death from any cause over our study's follow-up period (median: 85 months) associated with a one-unit increase in the Charlson index. Model 1 considered only the baseline Charlson index while adjusting for age, race/ethnicity and longitudinal exercise habits, with missing exercise values replaced by the last observation (HR: 1.4, 95% CI: 1.2, 1.7). Model 2 entered the Charlson index as a time-varying covariate, with missing values replaced by the last known observation, adjusting for the same covariates as Model 1 (HR: 1.3, 95% CI: 1.1, 1.5). Model 3 also considered acquired comorbidity but instead used multiply-imputed Charlson index values and exercise status in place of missing longitudinal values (HR: 1.4, 95% CI: 1.2, 1.6). We did not control for tumor and treatment characteristics because they are part of the causal pathway between comorbidity and mortality on our causal diagram (Figure 1). Statistical adjustment for such variables would be expected to attenuate the observed hazard ratio associating comorbidity with mortality by removing a portion of the total causal effect. We tested this expectation by additionally adjusting for stage, histologic grade, estrogen receptor status, surgery type, receipt of adjuvant tamoxifen, and receipt of adjuvant chemotherapy. Adjustment for these variables reduced the comorbidity hazard ratio in each of the three models by 5% or less.

Discussion

We followed 689 breast cancer survivors for a median of 85 months; 33 months longer than a similar previous study.⁸ We found that accounting only for baseline comorbidity gave approximately the same hazard ratio associating burden of comorbidity with all-cause mortality, compared to when comorbidity was regressed as a time-varying exposure (Hazard ratios: 1.4 and 1.3, respectively). Use of multiple imputation to populate missing values in longitudinal Charlson comorbidity data gave the same result (HR: 1.4). We consider our best estimate of the hazard ratio for a unit increase in Charlson index on the rate of all-cause mortality to be from Model 3, which used imputed values for all missing independent variables in the model. This estimate (HR: 1.4, 95% CI 1.2, 1.6) was consistent with the findings from an earlier study that examined the association between baseline Charlson index and all-cause mortality while controlling for age, primary treatment type, tumor stage, histologic grade and hormone receptor status,⁸ as well as a second study that examined only the impact of diabetes on all-cause mortality in breast cancer patients.¹²

Limitations

During our follow-up period, about 26% of subjects experienced an increase in comorbidity from baseline. Of those, approximately 80% had only a single-unit increase in Charlson index. These numbers indicate a relatively modest rate of comorbidity gain among cohort members. The present duration of follow-up—while the longest yet reported for a study of this association—may still be too short to capture an impact of longitudinal comorbidity on all-cause mortality rates. Our results indicate that a comorbidity assessment at the time of primary breast cancer treatment may provide sufficient short-term prognostic information (~7 years post-surgery) for older breast cancer survivors.

Additional analyses with breast cancer mortality as the outcome would be of great interest. We could not conduct an appropriately powered analysis focused on breast cancer-specific

mortality because the NDI registry does not yet contain cause of death data for all of the deceased subjects in our cohort.

The subjects in our cohort were predominately Caucasian (94%), so our results pertain mostly to women of that race. The poor representation of non-Caucasians in our cohort does not permit a rigorous evaluation of race/ethnicity as an effect modifier of the measured association between comorbidity and all-cause mortality.

Our results are susceptible to distortion by residual confounding, misclassification and selection bias. Our exposure, outcome, and covariate data are subject to varying degrees of misclassification. Some subjects in our study were likely better historians of their medical history than others. There were 359 instances in which subjects failed to report one or more persisting medical condition in their 27, 51 and 87 month interviews, with respect to their baseline report. Of the fifteen conditions that form the Charlson score, the most frequently under-reported at the 27-month interview—among those with a positive report for the condition at baseline—were heart failure (9%), diabetes (6%), stroke (5%), myocardial infarction (4%), connective tissue disease (4%) and pulmonary disease (3%). The remaining contributory conditions were under-reported with frequencies less than or equal to 2%. Under-reporting of medical history after the baseline interview was addressed by building monotonicity into the longitudinal Charlson index values. This method increased the sensitivity of comorbidity classification at the expense of specificity, which would cause over-estimation of Charlson index if subjects falsely reported having certain conditions at any interview point. While we cannot directly evaluate the extent of such over-estimation in our own data, prior validation studies have shown that Charlson scores derived from interview data have test-retest reliability of approximately 0.9,¹⁵ and are strongly correlated with scores derived from medical record review (correlation coefficient: 0.58, $P < 0.001$).¹⁹ Our results did not differ substantially when we did not force monotonicity onto longitudinal Charlson index values, allowing them to decrease over time, indicating that our reported hazard ratios were not substantially affected by this potential source of misclassification of comorbidity.

Misclassification of confounders, if non-differential with respect to outcome status, results in residual confounding.²⁰ Little if any misclassification is expected in the age and race/ethnicity variables, but exercise habits may be mis-reported by participants. Our measured exercise variable may also be an incomplete proxy for the conceptual entity for which we wished to control, which was routine physical activity that would affect the risk of both comorbid disease and all-cause mortality. The extent to which our measured exercise variable does not map to this concept informs the degree of residual confounding in our adjusted estimate of association. Adjustment for exercise decreased the crude hazard ratio associated with Charlson index by 2%, indicating a slight bias away from the null due to confounding by exercise habits. If exercise was non-differentially misclassified in our data, 2% would be an underestimate of the true magnitude of the upward confounding bias and the true adjusted hazard ratio would be lower than what we observed. Validation studies of specific physical activity instruments have shown significant correlations between older subjects' responses and objectively measured physiologic parameters indicating regular physical activity^{21, 22} as well as with results from "gold standard" doubly-labeled water experiments.²³ While our assessment of exercise habits relied on none of the particular instruments examined by the validation studies, our question to participants was detailed and specific in nature and should be of similar validity. Responses to this interview question are expected to conform reasonably well to the ideal concept for which we sought to adjust. We therefore do not expect residual confounding by exercise to be of a sufficient magnitude to explain our result completely.

Misclassification of vital status is unlikely, given the reliability of the National Death Index, Social Security Administration and Centers for Medicare and Medicaid Services death indices.

Approximately 94% of deaths in our cohort were ascertained from the NDI, which has consistently demonstrated high sensitivity and specificity (both nearly 100%) for vital status.^{20, 24} Approximately 5% of deaths were ascertained through the Social Security Administration database which, while inferior to the NDI, also exhibits favorable classification accuracy.²⁴ Proxy interviews and the CMS database contributed only one death each, and any flaws in these sources would not have substantially influenced our results.

We restricted our analytic sample to women in our cohort who had completed a baseline interview (3 months after primary breast cancer surgery). If completion of the baseline interview was an effect of both comorbidity (or its absence) and vital status, then selection bias could distort our observed association.²⁵ We believe the most likely scenario is that subjects with a greater comorbidity burden at enrollment were less likely to complete their 3-month interview, either because of their illness or because of death before the 3 month point. If this pattern is indeed the case, the selection bias would have the effect of lowering the observed association between comorbidity and all-cause mortality, and could not account for our result. In support of this pattern, we observed a 42% higher odds of dying among the cohort subjects who did not complete a baseline interview, compared to those who did (OR: 1.42, 95% CI: 1.00, 2.00). Our cohort also experienced loss to follow-up, which resulted in missing data in the exposure (comorbidity) and confounder (exercise) data. The sensitivity of our observed results to these losses was tested by modeling with multiply imputed values replacing the missing fields. Multiple imputation is an attractive alternative to carrying forward prior observations in longitudinal analyses; it yields results that incorporate uncertainty about the imputed values into confidence intervals.¹⁷ Examination of our survival analysis results (Table 3) shows that the confidence interval around the hazard ratio corresponding to the multiply imputed data is actually the narrowest, despite the additional uncertainty it contains. This counter-intuitive result is likely explained by the ability of this model to include 71 additional observations from subjects without baseline exercise data. Inclusion of these observations in the imputation model apparently increases precision more than the imputation decreases it.

In conclusion, we found that a unit increase in the Charlson index of comorbidity was associated with a 40% higher hazard of death from any cause among older survivors of early-stage female breast cancer. The same general result was observed whether or not we accounted for acquired comorbidities and missing data. The modest rate of comorbidity gain in our cohort may be responsible for the equivalent results between longitudinal and baseline-only accounting of comorbidity. Additional prognostic value of longitudinal comorbidity may become evident upon longer follow-up.

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Abbreviations

95% CI	95% confidence interval
HR	Hazard ratio
MCMC	Markov Chain Monte-Carlo
MI	Multiple imputation
BCS	Breast conserving surgery
RT	Radiation therapy
NDI	National Death Index

SSA	Social Security Administration
CMS	Centers for Medicare and Medicaid Services

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Figure 1.

Directed acyclic graph depicting hypothesized relationships among covariates. Boxes indicate variables identified by backdoor test as confounders requiring adjustment. “Therapy” and “Stage” denote breast cancer treatment choices and AJCC disease staging, respectively.

Figure 2.
Distribution of observed and imputed Charlson index values by interview month following primary breast cancer surgery.

Table 1

Formation of the Charlson index: Prevalent comorbid conditions for each subject were assigned weights according to the table. The sum of the weights was then used to form the ordinal Charlson index (Charlson index of 0: no comorbid conditions; Charlson index of 1: sum of weights equal to 1 or 2; Charlson index of 2: sum of weights equal to 3 or 4; Charlson index of 3: sum of weights ≥ 5).

Charlson Weight	Comorbid Conditions
0	No comorbid conditions
1	Heart attack or treated for heart failure Surgical treatment for peripheral vascular disease Stroke, blood clot, or transient ischemic attack without loss of limb function Asthma treated with medications Peptic ulcer disease diagnosed by endoscopy or barium swallow Diabetes treated with oral medication or insulin injections Rheumatoid arthritis treated with medications, lupus, or polymyalgia rheumatica Alzheimer's disease or other dementia
2	Stroke, blood clot, or transient ischemic attack with reduced arm or leg function Poor kidney function, high blood creatinine, ever used hemodialysis or peritoneal dialysis, or kidney transplant Diabetes with end-organ complications Diagnosed leukemia, lymphoma, or polycythemia vera
3	Cirrhosis or serious liver damage

Table 2

Observed baseline characteristics of the cohort (n=689)

	No. of Deaths	No. of Subjects	Total Person-days (%)
Age (years)			
65-69	33	176	395,769 (28)
70-79	112	383	822,089 (57)
> 79	73	130	215,425 (15)
Race/ethnicity			
Caucasian	197	643	1,353,934 (94)
African-American	15	34	58,903 (4.1)
Hispanic	1	3	5,748 (0.4)
Asian/Pacific Islander	0	1	2,669 (0.2)
Native American	1	1	916 (0.1)
Other	4	7	11,112 (0.8)
Baseline Charlson Index			
0	93	390	850,230 (59)
1	95	248	485,639 (34)
2	21	38	77,758 (5.4)
3	9	13	19,586 (1.4)
Baseline Exercise Status			
Exercises Regularly	83	350	767,999 (59)
Does Not Exercise Regularly	96	262	542,221 (41)
Enrollment Site			
Los Angeles	45	152	331,732 (23)
Rhode Island	64	174	355,070 (25)
Minnesota	65	190	384,647 (27)
North Carolina	44	173	361,834 (25)
AJCC[†] Stage			
I	95	351	749,254 (52)
IIA	64	207	441,773 (31)
IIB	41	103	193,505 (14)
IIIA	17	27	48,101 (3.4)
Surgical Treatment			
BCS, plus radiation therapy	46	218	496,136 (35)
BCS, no radiation therapy	42	111	220,916 (16)
Mastectomy	119	330	665,189 (47)
Other	9	19	31,292 (2.2)
Estrogen Receptor Status			
Positive	152	510	1,072,027 (76)
Negative	38	93	184,500 (13)
Unknown	25	76	152,627 (11)
Tamoxifen Prescription			
Ever prescribed	135	453	959,096 (67)

	No. of Deaths	No. of Subjects	Total Person-days (%)
Never prescribed	71	203	417,637 (29)
Unknown	12	33	56,550 (3.9)

[†] American Joint Committee on Cancer staging system

Table 3

Cox proportional hazards models of all-cause mortality as a function of baseline or acquired comorbidity

Model	Parameter	Hazard Ratio [*]	95% CI	P-value
(1) Baseline Charlson	Charlson index	1.4	1.2, 1.7	0.0004
	Age	2.4	1.9, 3.0	<.0001
	Race/ethnicity	1.6	1.0, 2.7	0.06
	Exercise	1.1	0.7, 1.3	0.19
(2) Time-varying Charlson index; missing values replaced by last known value	Charlson index	1.3	1.1, 1.5	0.003
	Age	2.4	1.9, 3.0	<.0001
	Race/ethnicity	1.7	1.0, 2.9	0.04
	Exercise	1.1	1.0, 1.4	0.14
(3) Time-varying Charlson index; missing values multiply imputed [†]	Charlson index	1.4	1.2, 1.6	0.0003
	Age	2.3	1.9, 2.8	<.0001
	Race/ethnicity	1.8	1.1, 2.8	0.02
	Exercise	1.2	0.9, 1.6	0.045

^{*} Comparisons for hazard ratios; Charlson index: 1-unit increase in ordinal value; Age: 10 year increase; Race/ethnicity: non-Caucasian vs. Caucasian; Exercise: regular exercisers vs. non-regular exercisers.

[†] Missing values for exercise habits were also multiply imputed. Hazard ratio estimates and 95% confidence intervals were pooled over five imputations. P-values are conservatively reported as the highest from among the five imputation models.