

Bridging The Age Gap: observational cohort study of effects of chemotherapy and trastuzumab on recurrence, survival and quality of life in older women with early breast cancer

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Supplementary materials

Supplementary Table 1 - List of participating sites.

	Site Name	Local PI
1	Sheffield	Lynda Wyld and Matt Winter
2	Barnsley	Julia Dicks
3	Doncaster	Clare Rogers
4	Milton Keynes	Amanda Taylor
5	Scunthorpe and Grimsby	Rajesh Vijn (Scunthorpe), Jenny Smith (Grimsby)
6	Leicester	Monika Kaushik
7	Derby	Kwok Leung Cheung
8	East Lancashire	Julie Iddon
9	Harrogate	Matthew Adelekan
10	St Helens and Knowsley	Riccardo Audisio
11	York	Rana Nasr (York and Scarborough)
12	Liverpool	Chris Holcombe
13	Airedale	Claire Murphy
14	Leeds	Kieran Horgan
15	Bradford	Rick Linforth
16	Cardiff	Helen Sweetland
17	Aneurin Bevan Health Board	Simon Waters (Royal Gwent), Theresa Howe (Nevill Hall)
18	Royal Lancaster	Rishi Parmeshwar
19	Coventry	Abigail Tomlins
20	Grantham	Anzors Gvaramadze
21	Lincoln	Anzors Gvaramadze
22	Pilgrim	Anzors Gvaramadze
23	Hull	Peter Kneeshaw
24	Nottingham	Lisa Whisker
25	Southport	Anwar Haq
26	Leighton	Vanessa Pope
27	Royal Marsden	Jenny Rusby
28	Cheltenham General	Sarah Vestey
29	Guys and St Thomas	Michael Douek
30	Dorset County	Caroline Osborne
31	Mid Essex	Sascha Miles-Dua
32	Mid Yorkshire	Jay Naik
33	Bristol	Zoe Winters
34	Chesterfield	Iman Azmy
35	Rotherham	Inder Kumar
36	Darent Valley	Seema Seetharam
37	Kingston	Karyn Shenton
38	Colchester	Mukesh Mukesh

39	Yeovil	Caroline Osborne
40	Croydon	Sanjay Joshi
41	North Tees	Colm Hennessy
42	South Tees	Imtiaz Cheema
43	Luton and Dunstable	Mei-Lin Ah-See
44	Weston General	Rachel Ainsworth
45	Tameside	Stephanie Ridgway
46	Macclesfield	Lisa Barraclough
47	Wrightington, Wigan and Leigh	Angela Power
48	Birmingham	Fiona Hoar
49	Kings Mill	Rebecca Boulton
50	Wythenshawe	Nigel Bundred
51	Aintree	Peter Robson
52	Brighton	Gargi Patel
53	St Margaret's	Ashraf Patel
54	St Marys	Steve Parker
55	Oxford	Asha Adwani
56	Frimley and Wexham	Ruth Davis (Wexham), Raouf Daoud (Frimley)

Supplementary Table 2a - Definition of risk of breast cancer recurrence based on tumour characteristics on diagnostic biopsy or surgical specimen.

Tumour characteristics	Risk of recurrence	
	High*	Low
ER	Negative	Positive
HER2	Positive	Negative
Grade	3	1-2
Nodal involvement	Yes	No
Oncotype DX Recurrence Score	≥25	<25

**high risk is defined by the presence of ≥1 of the features enlisted.*

Supplementary Table 2b – Definition of fitness categories were determined. Overall scores were defined: Fit: 0-2. Vulnerable: 3-8. Frail: 9+.

Domain	Range	Score		
		0	1	2
ECOG PS	0-4	0-1	2	3-4
ADL	0-10	20	19	≤18
IADL	0-8	8	7	≤6
Charlson comorbidity index	-	0-1	-	≥2
Prescribed medications (excluding vitamins/minerals)	-	≤3	≥4	-
APSGA		0-3	4-8	≥9
MMSE	0-30	≥24	20-24	<20

Supplementary Table 3 - Baseline patient characteristics by receipt of chemotherapy.

		No Chemotherapy N = 2414	Chemotherapy N = 397
Participation level	Full	1789 (74.1%)	322 (81.1%)
	Partial	550 (22.8%)	71 (17.9%)
	Consultee	75 (3.1%)	4 (1.0%)
Age	n	2414	397
	Mean (SD)	76.98 (5.25)	73.62 (3.30)
	Median (IQR)	76.00 (73.00, 80.00)	73.00 (71.00, 76.00)
	Min, Max	69, 95	69, 87
Charlson comorbidity index (no age)	n	2322	385
	Mean (SD)	1.07 (1.33)	0.81 (1.10)
	Median (IQR)	1.00 (0.00, 2.00)	0.00 (0.00, 2.00)
	Min, Max	0, 9	0, 6
Charlson calculated probability	n	2322	385
	Mean (SD)	0.45 (0.30)	0.56 (0.27)
	Median (IQR)	0.53 (0.21, 0.77)	0.77 (0.21, 0.77)
	Min, Max	0, 0.77	0, 0.77
Number of concurrent medications	n	2116	330
	Mean (SD)	4.13 (2.66)	3.63 (2.49)
	Median (IQR)	4.00 (2.00, 6.00)	3.00 (2.00, 5.00)
	Min, Max	0, 18	0, 14
ADL category	No dependency	1683 (69.7%)	321 (80.9%)
	Mild dependency	274 (11.4%)	34 (8.6%)
	Moderate/severe dependency	262 (10.9%)	16 (4.0%)
	Unknown	195 (8.1%)	26 (6.5%)
IADL category	No dependency	1737 (72.0%)	332 (83.6%)
	Mild dependency	221 (9.2%)	28 (7.1%)
	Moderate/severe dependency	248 (10.3%)	10 (2.5%)
	Unknown	208 (8.6%)	27 (6.8%)
MMSE category	Normal function	2133 (88.4%)	361 (90.9%)
	Mild impairment	220 (9.1%)	28 (7.1%)
	Moderate impairment	30 (1.2%)	6 (1.5%)
	Severe	31 (1.3%)	2 (0.5%)
APG SGA category	Low	1864 (77.2%)	316 (79.6%)
	Moderate	249 (10.3%)	39 (9.8%)
	High	36 (1.5%)	4 (1.0%)
	Unknown	265 (11.0%)	38 (9.6%)
ECOG performance status	0	1632 (67.6%)	312 (78.6%)
	1	544 (22.5%)	63 (15.9%)
	2	77 (3.2%)	3 (0.8%)
	3	34 (1.4%)	2 (0.5%)
	4	1 (0.0%)	0 (0.0%)
	Unknown	126 (5.2%)	17 (4.3%)

Supplementary Table 4 - Postoperative tumour characteristics by receipt of chemotherapy.

		No Chemotherapy	Chemotherapy
		N = 2414	N = 397
Main side	Right	1128 (46.7%)	177 (44.6%)
	Left	1286 (53.3%)	220 (55.4%)
Tumour size (mm)	n	2365	387
	Mean (SD)	24.2 (15.8)	32.8 (20.5)
	Median (IQR)	20.0 (14.0, 30.0)	29.0 (21.0, 40.0)
	Min, Max	0, 155	0, 210
Tumour size (mm)	≤ 20	1183 (49.0%)	96 (24.2%)
	21-50	1043 (43.2%)	242 (61.0%)
	> 50	139 (5.8%)	49 (12.3%)
	Unknown	49 (2.0%)	10 (2.5%)
Nodal status	pN0-1mi	1726 (71.5%)	187 (47.1%)
	pN1	495 (20.5%)	117 (29.5%)
	pN2	95 (3.9%)	52 (13.1%)
	pN3	46 (1.9%)	32 (8.1%)
	pNx	52 (2.2%)	9 (2.3%)
Grade	Grade 1	377 (15.6%)	4 (1.0%)
	Grade 2	1355 (56.1%)	130 (32.7%)
	Grade 3	618 (25.6%)	247 (62.2%)
	Unknown	64 (2.7%)	16 (4.0%)
Histology	Ductal NST	1534 (63.5%)	281 (70.8%)
	Lobular carcinoma	321 (13.3%)	54 (13.6%)
	Tubular carcinoma	29 (1.2%)	0 (0.0%)
	Mucinous carcinoma	70 (2.9%)	1 (0.3%)
	Other	235 (9.7%)	31 (7.8%)
	Unknown	225 (9.3%)	30 (7.6%)
ER positive	Negative	240 (9.9%)	132 (33.2%)
	Positive	2101 (87.0%)	253 (63.7%)
	Unknown	73 (3.0%)	12 (3.0%)
HER2 status	Negative	2050 (84.9%)	222 (55.9%)
	Inconclusive	19 (0.8%)	3 (0.8%)
	Positive	173 (7.2%)	159 (40.1%)
	Unknown	172 (7.1%)	13 (3.3%)
Oncotype Dx test performed	No	428 (17.7%)	36 (9.1%)
	Yes	35 (1.4%)	6 (1.5%)
	Not Applicable	571 (23.7%)	261 (65.7%)
	Unknown	1380 (57.2%)	94 (23.7%)
Breast surgery	Wide local excision	1433 (59.4%)	165 (41.5%)
	Therapeutic mastoplasty / breast reshaping after WLE	33 (1.4%)	18 (4.5%)
	Mastectomy	860 (35.6%)	189 (47.6%)
	Mastectomy and reconstruction	25 (1.0%)	12 (3.0%)
	Other	16 (0.7%)	4 (1.0%)
	Unknown	47 (1.9%)	9 (2.3%)

		No Chemotherapy	Chemotherapy
		N = 2414	N = 397
Axillary surgery	Axillary sample	76 (3.1%)	12 (3.0%)
	Axillary clearance	274 (11.4%)	140 (35.3%)
	Sentinel lymph node biopsy	1770 (73.3%)	210 (52.9%)
	Internal mammary node biopsy	1 (0.0%)	0 (0.0%)
	No axillary surgery	73 (3.0%)	7 (1.8%)
	Unknown	220 (9.1%)	28 (7.1%)

Supplementary Table 5 - Covariate balance in the final matched dataset: chemotherapy vs no chemotherapy.

		Chemotherapy	No Chemotherapy
		N = 200	N = 350
Age	n	200	350
	Mean (SD)	73.48 (2.91)	74.36 (3.06)
	Median (IQR)	73.00 (71.00, 76.00)	74.00 (72.00, 77.00)
	Min, Max	70, 80	69, 80
aPG-SGA	Low	173 (86.5%)	302 (86.3%)
	Moderate	24 (12.0%)	45 (12.9%)
	High	3 (1.5%)	3 (0.9%)
ADL	No dependency	162 (81.0%)	273 (78.0%)
	Mild dependency	26 (13.0%)	46 (13.1%)
	Moderate/severe dependency	12 (6.0%)	31 (8.9%)
iADL	No dependency	174 (87.0%)	299 (85.4%)
	Mild dependency	19 (9.5%)	31 (8.9%)
	Moderate/severe dependency	7 (3.5%)	20 (5.7%)
MMSE	Normal function	182 (91.0%)	317 (90.6%)
	Mild impairment	15 (7.5%)	28 (8.0%)
	Moderate impairment	3 (1.5%)	5 (1.4%)
CCI	0-1	176 (88.0%)	301 (86.0%)
	≥2	24 (12.0%)	49 (14.0%)
Medications	3 or fewer	109 (54.5%)	172 (49.1%)
	4 or more	91 (45.5%)	178 (50.9%)
ECOG	Low	195 (97.5%)	339 (96.9%)
	Moderate	3 (1.5%)	6 (1.7%)
	High	2 (1.0%)	5 (1.4%)
NPI	Moderate	137 (68.5%)	245 (70.0%)
	Good	10 (5.0%)	17 (4.9%)
	Poor	53 (26.5%)	88 (25.1%)
HER2	Negative	139 (69.5%)	269 (76.9%)
	Positive	61 (30.5%)	81 (23.1%)

Supplementary Table 6 - Mortality status for HER2-positive patients and ER-negative patients by use of chemotherapy.

		No Chemotherapy	Chemotherapy	Total
HER2+	n	170	156	326
	Died	45 (26.5%)	19 (12.2%)	64 (19.6%)
	n	169	156	325
	Died of breast cancer	24 (14.2%)	12 (7.7%)	36 (11.1%)
ER-	n	237	132	369
	Died	92 (38.8%)	20 (15.2%)	112 (30.4%)
	n	234	131	365
	Died of breast cancer	56 (23.9%)	13 (9.9%)	69 (18.9%)

Supplementary Table 7 - Toxicity in patients receiving chemotherapy (n=397)

Supplementary Table 7a – Adverse event rates according in the overall chemotherapy population and according to level of participation.

	Consultee	Full	Partial	Total
	N = 4	N = 322	N = 71	N = 397
Allergic reaction to chemotherapy agents	0 (0%)	21 (7%)	5 (7%)	26 (7%)
Anaemia	2 (50%)	69 (21%)	14 (20%)	85 (21%)
Fatigue	3 (75%)	231 (72%)	49 (69%)	283 (71%)
Hair thinning	2 (50%)	205 (64%)	42 (59%)	249 (63%)
Infection	1 (25%)	103 (32%)	28 (39%)	132 (33%)
Low white cell count	2 (50%)	76 (24%)	19 (27%)	97 (24%)
Nausea	3 (75%)	134 (42%)	30 (42%)	167 (42%)
Thrombocytopenia	3 (75%)	19 (6%)	7 (10%)	29 (7%)

Supplementary Table 7b - Adverse event rates according to CTCAE grading.

	Worse CTCAE grading	Individuals
Allergic reactions	1	7/26 (26.9%)
	2	9/26 (34.6%)
	3	2/26 (7.7%)
	4	1/26 (3.8%)
	Missing	7/26 (26.9%)
Anaemia	1	29/85 (34.1%)
	2	25/85 (29.4%)
	3	2/85 (2.4%)
	4	1/85 (1.2%)
	Missing	28/85 (32.9%)
Fatigue	1	95/283 (33.6%)
	2	75/283 (26.5%)
	3	26/283 (9.2%)
	4	1/283 (0.4%)
	Missing	86/283 (30.4%)
Alopecia	1	60/249 (24.1%)
	2	114/249 (45.8%)
	Missing	75/249 (30.1%)
Infection	2	49/132 (37.1%)
	3	44/132 (33.3%)
	4	6/132 (4.5%)
	Missing	33/132 (25.0%)
Low white cell count	1	16/97 (16.5%)
	2	24/97 (24.7%)
	3	11/97 (11.3%)
	4	11/97 (11.3%)
	Missing	35/97 (36.1%)

Nausea	1	84/167 (50%)
	2	31/167 (19%)
	3	3/167 (2%)
	Missing	49/167 (29%)
Thrombocytopenia	1	17/29 (59%)
	2	4/29 (14%)
	Missing	8/29 (28%)

Supplementary Table 8 - Mean scores and 95% confidence intervals (CIs) adjusted for baseline score for the EQ-5D-5L scale at each timepoint in chemotherapy versus no chemotherapy cohorts.

Domain	Time point	Chemotherapy	No Chemotherapy	Adjusted Mean Difference (95% CI)	P-value		
Score	Baseline	n	335	980			
		Mean (SD)	0.8769 (0.1327)	0.8693 (0.1489)	-	-	
	6 weeks	n	299	807	0.0130 (-0.0030, 0.0289)		
		Mean (SD)	0.8409 (0.1414)	0.8242 (0.1572)	-0.0028 (-0.0231, 0.0175)	0.112	
	6 months	n	279	760	-0.0013 (-0.0228, 0.0201)		
		Mean (SD)	0.8247 (0.1767)	0.8241 (0.1721)	0.0114 (-0.0143, 0.0372)	0.789	
	12 months	n	261	659	0.0001 (-0.0286, 0.0288)		
		Mean (SD)	0.8274 (0.1639)	0.8185 (0.1753)	0.0130 (-0.0030, 0.0289)	0.903	
	18 months	n	224	556	-0.0028 (-0.0231, 0.0175)		
		Mean (SD)	0.8186 (0.1937)	0.8088 (0.1910)	-0.0013 (-0.0228, 0.0201)	0.384	
	24 months	n	185	474	0.0114 (-0.0143, 0.0372)		
		Mean (SD)	0.8013 (0.1787)	0.8020 (0.1968)		0.994	
	VAS	Baseline	n	324	951		
			Mean (SD)	78.9 (16.3)	76.9 (16.6)	-	-
6 weeks		n	296	793			
		Mean (SD)	74.5 (17.4)	74.9 (17.0)	-1.44 (-3.52, 0.64)	0.176	
6 months		n	280	757			
		Mean (SD)	70.1 (18.0)	75.3 (16.7)	-6.57 (-8.74, -4.40)	<0.001	
12 months		n	256	656			
		Mean (SD)	76.7 (15.8)	74.8 (17.6)	0.72 (-1.60, 3.05)	0.541	
18 months		n	230	549			
		Mean (SD)	74.9 (17.6)	73.6 (18.3)	0.92 (-1.78, 3.63)	0.503	
24 months		n	185	479			
		Mean (SD)	74.7 (16.3)	72.7 (18.2)	1.48 (-1.41, 4.36)	0.315	

Supplementary figures

Supplementary Figure 1

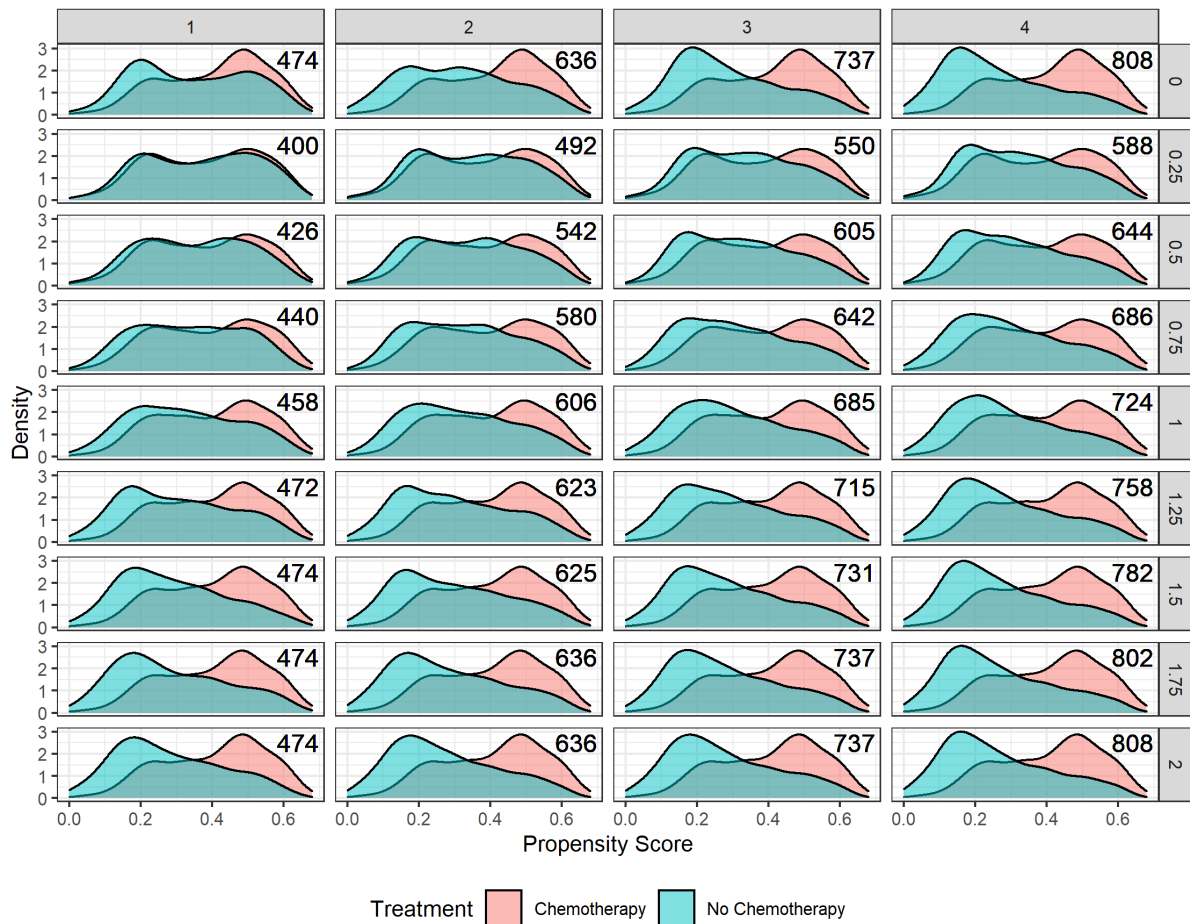
Logistic regression was used to calculate propensity scores for treatment allocation. The covariates included in the model were measures of functionality (ADL, IADL, MMSE, ECOG), nutritional status (nutrition (abridged PG-SGA), comorbidities (CCI, number of medications) and age. The models were built sequentially as follows:

- i) Using scores on their original scale and included patients in whom all scores were completed.
- ii) Using the categorised versions of the functionality, nutrition and comorbidity again for patients with all scores; age was retained as a continuous term.
- iii) As ii) including additional patients that could be classified but for whom the score itself was incomplete.

i) and ii) allowed a comparison of models based on categorised and uncategorised scores in order to establish how much information was lost by the categorisations; these were fitted the same participants. Models ii) and iii) differed in the number of individuals available for analysis, since completed inventories could be categorised for some participants. To illustrate taking the IADL, if seven of the eight questions were answered the total score is unknown, but the risk category could be assigned as "high risk" if the answers included two or more limitations. Models i) and ii) performed similarly as demonstrated by the AIC and c-statistics, meaning the simpler categorical model was adequate for creating the propensity scores.

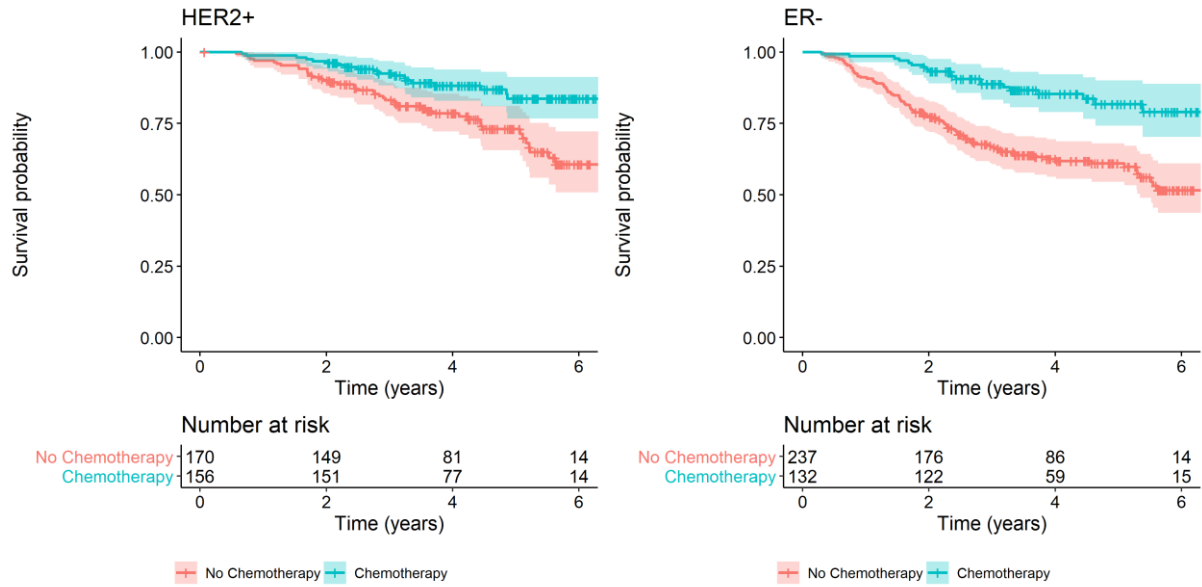
The propensity scores were then used to match chemotherapy patients to patients who did not receive chemotherapy up to a 1:3 ratio. A calliper of 0.25 times the standard deviation of the propensity scores was used to ensure participants were closely matched. This ratio and calliper were chosen based on an examination of the propensity score overlaps for several combinations of ratios and callipers. The figure below shows the overlap in the propensity score for matched sets with different callipers and ratios. Supplementary Table 5 shows the balance achieved in the final matched dataset.

Propensity score overlap and number of observations for matched groups with differing ratios (y-axis) and callipers (x-axis): chemotherapy vs no chemotherapy.

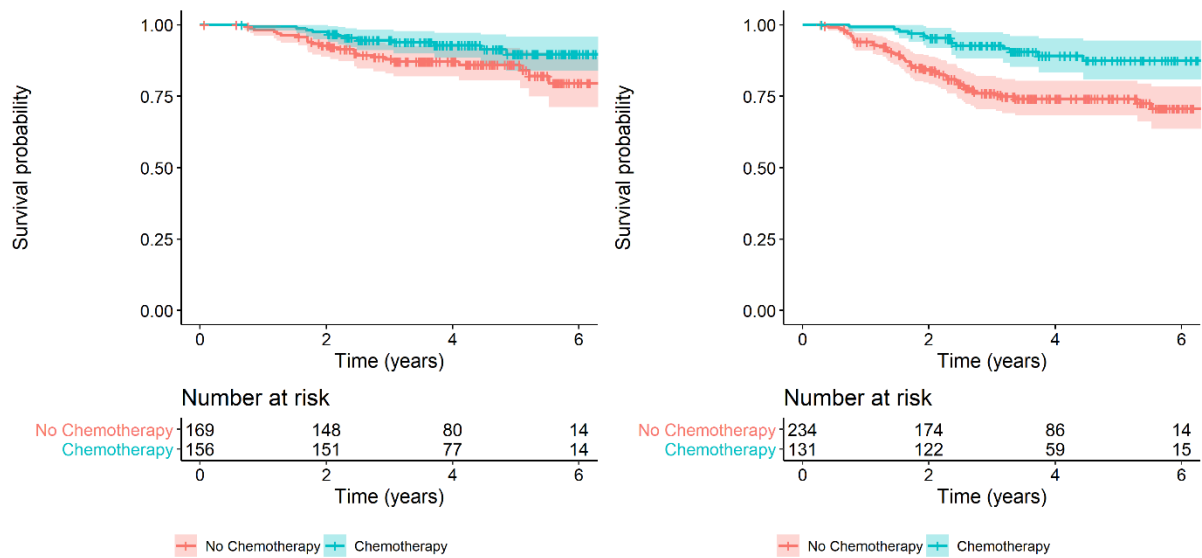


Supplementary Figure 2 - Kaplan-Meier plots for overall survival (8a) and breast cancer specific survival (8b) for HER2-positive and oestrogen receptor (ER)-negative patients by use of chemotherapy in unmatched population.

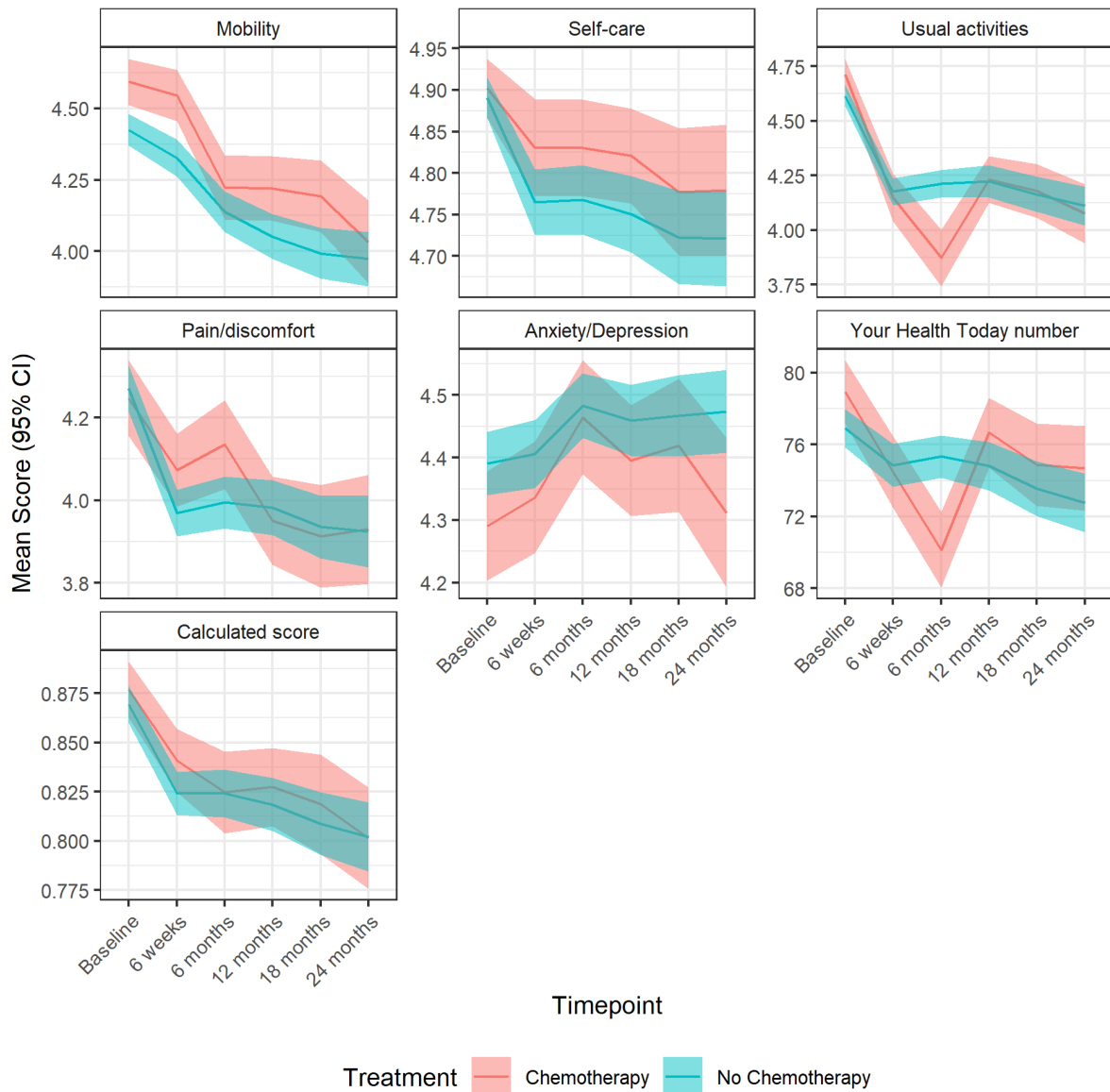
8a.



8b.



Supplementary Figure 3 – Mean (95% CI) scores over time points for the chemotherapy versus no chemotherapy population measured on the EQ-5D-5L scale.*



*the calculated score is a single summary number (index value) which reflects the health state in the context of the preferences of the general population of a country/region and is derived by applying a formula attaching weights to each of the levels in each dimension as per the EQ-5D-5L User Guide.

Supplementary Figure 4 – Mean (95% CI) EQ-5D-5L usual activities score over timepoints for the matched chemotherapy vs no chemotherapy population.

