

Supplementary appendix

Prognostic relation of body mass index on extended aromatase inhibition treatment in postmenopausal patients with estrogen receptor positive breast cancer: a retrospective analysis of the SOLE trial

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Abbreviations

Initials	Meaning
BC	Breast cancer
BCFI	Breast cancer free interval
BMI	Body mass index
CCI	Crude cumulative incidence
CI	Confidence interval
DFS	Disease free survival
DM	Distant metastasis
DR	Distant recurrence
DRFI	Distant recurrence free interval
ER	Estrogen receptor
FFPE	Formalin-fixed, Paraffin-embedded
ITT	Intention to treat
OS	Overall survival
RCS	Restricted cubic splines
RR	Risk ratio

Supplementary Tables

Supplementary Table 1: BMI, age and menopausal status according to treatment arm

		SERM only Nr patients (%)	SERM & AI Nr patients (%)	AI only Nr patients (%)
BMI category at diagnosis	Normal & underweight	273 (41.5)	584 (40.7)	535 (35.4)
	Overweight	239 (36.3)	513 (35.7)	563 (37.2)
	Obese	146 (22.2)	339 (23.6)	414 (27.4)
Age category at randomization	< 55	358 (54.4)	412 (28.7)	219 (14.5)
	55-59	130 (19.8)	322 (22.4)	304 (20.1)
	60-64	71 (10.8)	267 (18.6)	349 (23.1)
	65-69	48 (7.3)	243 (16.9)	299 (19.8)
	70+	51 (7.8)	192 (13.4)	341 (22.6)
Menopausal status at diagnosis	Premenopausal	271 (41.6)	304 (21.2)	151 (10.0)
	Perimenopausal	29 (4.4)	59 (4.1)	43 (2.8)
	Postmenopausal	352 (54.0)	1069 (74.7)	1316 (87.2)
	Missing	6	4	2

Supplementary Table 2: Number of patients and events per subgroup of patients

	Prior ET	Treatment arm	Nr of patients	Nr of events	Nr of competing events
DRFI	SERM only	Continuous letrozole	337	26	24
		Intermittent letrozole	333	30	29
	SERM and AI	Continuous letrozole	768	66	80
		Intermittent letrozole	816	61	106
	AI only	Continuous letrozole	759	85	67
		Intermittent letrozole	780	69	92
BCFI	SERM only	Continuous letrozole	337	36	14
		Intermittent letrozole	333	42	17
	SERM and AI	Continuous letrozole	768	88	58
		Intermittent letrozole	816	90	77
	AI only	Continuous letrozole	759	101	51
		Intermittent letrozole	780	96	65
DFS	SERM only	Continuous letrozole	337	50	Not applicable
		Intermittent letrozole	333	59	
	SERM and AI	Continuous letrozole	768	146	
		Intermittent letrozole	816	167	
	AI only	Continuous letrozole	759	152	
		Intermittent letrozole	780	161	
OS	SERM only	Continuous letrozole	337	23	Not applicable
		Intermittent letrozole	333	28	
	SERM and AI	Continuous letrozole	768	84	
		Intermittent letrozole	816	86	
	AI only	Continuous letrozole	759	92	
		Intermittent letrozole	780	81	

Supplementary Table 3: DRFI – model details for the main event

Categorical BMI

BMI	Pre.treatment	Treatment	Risk.Ratios
Overweight vs Normalweight	SERM only	Continuous	1.59 (0.97, 2.6)
Obese vs Normalweight	SERM only	Continuous	1.23 (0.68, 2.23)
Overweight vs Normalweight	SERM only	Intermittent	2.3 (1.49, 3.57)
Obese vs Normalweight	SERM only	Intermittent	0.56 (0.31, 1.01)
Overweight vs Normalweight	Both SERM and AI	Continuous	0.54 (0.37, 0.77)
Obese vs Normalweight	Both SERM and AI	Continuous	0.61 (0.42, 0.9)
Overweight vs Normalweight	Both SERM and AI	Intermittent	0.84 (0.58, 1.2)
Obese vs Normalweight	Both SERM and AI	Intermittent	2.31 (1.41, 3.78)
Overweight vs Normalweight	AI only	Continuous	0.64 (0.46, 0.89)
Obese vs Normalweight	AI only	Continuous	0.65 (0.48, 0.89)
Overweight vs Normalweight	AI only	Intermittent	0.38 (0.29, 0.5)
Obese vs Normalweight	AI only	Intermittent	0.63 (0.46, 0.87)

p-value for non-linearity of Age: 0.0161

Continuous BMI

p-value for non-linearity of Age: <0.0001

p-value for non-linearity of BMI: <0.0001

Supplementary Table 4: DRFI – model details for the competing event

Categorical BMI

BMI	Pre.treatment	Treatment	Risk.Ratios
Overweight vs Normalweight	SERM only	Continuous	0.49 (0.24, 1.03)
Obese vs Normalweight	SERM only	Continuous	1.07 (0.51, 2.24)
Overweight vs Normalweight	SERM only	Intermittent	1.25 (0.72, 2.17)
Obese vs Normalweight	SERM only	Intermittent	1.45 (0.79, 2.64)
Overweight vs Normalweight	Both SERM and AI	Continuous	0.88 (0.69, 1.13)
Obese vs Normalweight	Both SERM and AI	Continuous	0.58 (0.4, 0.85)
Overweight vs Normalweight	Both SERM and AI	Intermittent	0.72 (0.53, 0.98)
Obese vs Normalweight	Both SERM and AI	Intermittent	1.02 (0.8, 1.3)
Overweight vs Normalweight	AI only	Continuous	0.88 (0.63, 1.25)
Obese vs Normalweight	AI only	Continuous	0.87 (0.65, 1.17)
Overweight vs Normalweight	AI only	Intermittent	0.99 (0.76, 1.29)
Obese vs Normalweight	AI only	Intermittent	0.94 (0.65, 1.35)

p-value for non-linearity of Age: 0.0342

Continuous BMI

p-value for non-linearity of Age: 0.605

p-value for non-linearity of BMI: <0.0001

Supplementary Table 5: DRFI – exploratory model (with duration prior AI) details for the main event

Categorical BMI

BMI	Pre.treatment	Treatment	Risk.Ratios
Overweight vs Normalweight	SERM only	Continuous	1.8 (1.32 , 2.45)
Obese vs Normalweight	SERM only	Continuous	1.25 (0.87 , 1.78)
Overweight vs Normalweight	SERM only	Intermittent	2.36 (1.69 , 3.28)
Obese vs Normalweight	SERM only	Intermittent	0.69 (0.5 , 0.93)
Overweight vs Normalweight	Both SERM and AI	Continuous	0.66 (0.53 , 0.81)
Obese vs Normalweight	Both SERM and AI	Continuous	0.7 (0.55 , 0.88)
Overweight vs Normalweight	Both SERM and AI	Intermittent	0.91 (0.74 , 1.12)
Obese vs Normalweight	Both SERM and AI	Intermittent	2.03 (1.54 , 2.69)
Overweight vs Normalweight	AI only	Continuous	0.73 (0.63 , 0.84)
Obese vs Normalweight	AI only	Continuous	0.8 (0.68 , 0.93)
Overweight vs Normalweight	AI only	Intermittent	0.43 (0.38 , 0.5)
Obese vs Normalweight	AI only	Intermittent	0.66 (0.56 , 0.77)

p-value for non-linearity of Age: 0.39

Continuous BMI

p-value for non-linearity of Age: 0.006

p-value for non-linearity of BMI: <0.0001

Supplementary Table 6: DRFI – exploratory model (with duration prior AI) details for the competing event

Categorical BMI

BMI	Pre.treatment	Treatment	Risk.Ratios
Overweight vs Normalweight	SERM only	Continuous	0.58 (0.39 , 0.87)
Obese vs Normalweight	SERM only	Continuous	0.87 (0.53 , 1.43)
Overweight vs Normalweight	SERM only	Intermittent	1.39 (1.01 , 1.92)
Obese vs Normalweight	SERM only	Intermittent	1.61 (1.15 , 2.25)
Overweight vs Normalweight	Both SERM and AI	Continuous	0.94 (0.8 , 1.09)
Obese vs Normalweight	Both SERM and AI	Continuous	0.68 (0.55 , 0.84)
Overweight vs Normalweight	Both SERM and AI	Intermittent	0.72 (0.6 , 0.87)
Obese vs Normalweight	Both SERM and AI	Intermittent	1.15 (0.9 , 1.47)
Overweight vs Normalweight	AI only	Continuous	0.83 (0.69 , 0.99)
Obese vs Normalweight	AI only	Continuous	0.87 (0.74 , 1.02)
Overweight vs Normalweight	AI only	Intermittent	0.97 (0.84 , 1.11)
Obese vs Normalweight	AI only	Intermittent	1 (0.8 , 1.25)

p-value for non-linearity of Age: <0.0001

Continuous BMI

p-value for non-linearity of Age: 0.02

p-value for non-linearity of BMI: <0.0001

Supplementary Table 7: BCFI – model details for the main event
Categorical BMI

BMI	Pre.treatment	Treatment	Risk.Ratios
Overweight vs Normalweight	SERM only	Continuous	1.1 (0.69, 1.76)
Obese vs Normalweight	SERM only	Continuous	0.69 (0.39, 1.24)
Overweight vs Normalweight	SERM only	Intermittent	2.33 (1.38, 3.94)
Obese vs Normalweight	SERM only	Intermittent	0.73 (0.48, 1.11)
Overweight vs Normalweight	Both SERM and AI	Continuous	0.59 (0.45, 0.78)
Obese vs Normalweight	Both SERM and AI	Continuous	0.5 (0.37, 0.68)
Overweight vs Normalweight	Both SERM and AI	Intermittent	1.14 (0.83, 1.56)
Obese vs Normalweight	Both SERM and AI	Intermittent	3.13 (1.85, 5.31)
Overweight vs Normalweight	AI only	Continuous	0.75 (0.57, 0.97)
Obese vs Normalweight	AI only	Continuous	0.8 (0.59, 1.07)
Overweight vs Normalweight	AI only	Intermittent	0.49 (0.38, 0.63)
Obese vs Normalweight	AI only	Intermittent	0.67 (0.5, 0.89)

p-value for non-linearity of Age: 0.2268

Continuous BMI

p-value for non-linearity of Age: 0.2585

p-value for non-linearity of BMI: <0.0001

Supplementary Table 8: BCFI – model details for the competing event

Categorical BMI

BMI	Pre.treatment	Treatment	Risk.Ratios
Overweight vs Normalweight	SERM only	Continuous	1.52 (0.55, 4.22)
Obese vs Normalweight	SERM only	Continuous	4.92 (1.76, 13.77)
Overweight vs Normalweight	SERM only	Intermittent	0.83 (0.44, 1.58)
Obese vs Normalweight	SERM only	Intermittent	1.48 (0.75, 2.95)
Overweight vs Normalweight	Both SERM and AI	Continuous	0.9 (0.68, 1.18)
Obese vs Normalweight	Both SERM and AI	Continuous	0.64 (0.41, 0.98)
Overweight vs Normalweight	Both SERM and AI	Intermittent	0.59 (0.4, 0.87)
Obese vs Normalweight	Both SERM and AI	Intermittent	0.75 (0.56, 0.99)
Overweight vs Normalweight	AI only	Continuous	0.86 (0.58, 1.27)
Obese vs Normalweight	AI only	Continuous	0.76 (0.55, 1.05)
Overweight vs Normalweight	AI only	Intermittent	0.73 (0.56, 0.96)
Obese vs Normalweight	AI only	Intermittent	1.34 (0.84, 2.13)

p-value for non-linearity of Age: 0.0181

Continuous BMI

p-value for non-linearity of Age: 0.0088

p-value for non-linearity of BMI: 8e-04

Supplementary Table 9: DFS – model details

Categorical BMI

BMI	Pre.treatment	Treatment	Risk.Ratios
Overweight vs Normalweight	SERM only	Continuous	1.24 (0.82, 1.89)
Obese vs Normalweight	SERM only	Continuous	1 (0.59, 1.69)
Overweight vs Normalweight	SERM only	Intermittent	1.69 (1.15, 2.47)
Obese vs Normalweight	SERM only	Intermittent	1.01 (0.74, 1.39)
Overweight vs Normalweight	Both SERM and AI	Continuous	0.8 (0.62, 1.03)
Obese vs Normalweight	Both SERM and AI	Continuous	0.67 (0.5, 0.9)
Overweight vs Normalweight	Both SERM and AI	Intermittent	0.98 (0.78, 1.24)
Obese vs Normalweight	Both SERM and AI	Intermittent	1.76 (1.3, 2.39)
Overweight vs Normalweight	AI only	Continuous	0.82 (0.69, 0.98)
Obese vs Normalweight	AI only	Continuous	0.97 (0.78, 1.21)
Overweight vs Normalweight	AI only	Intermittent	0.73 (0.63, 0.85)
Obese vs Normalweight	AI only	Intermittent	0.9 (0.73, 1.11)

p-value for non-linearity of Age: 0.0336

Continuous BMI

p-value for non-linearity of Age: 0.0762

p-value for non-linearity of BMI: <0.0001

Supplementary Table 10: OS – model details

Categorical BMI

BMI	Pre.treatment	Treatment	Risk.Ratios
Overweight vs Normalweight	SERM only	Continuous	0.94 (0.81, 1.1)
Obese vs Normalweight	SERM only	Continuous	1.19 (1.02, 1.38)
Overweight vs Normalweight	SERM only	Intermittent	1.3 (0.61, 2.73)
Obese vs Normalweight	SERM only	Intermittent	1.63 (0.77, 3.45)
Overweight vs Normalweight	Both SERM and AI	Continuous	1.08 (0.72, 1.61)
Obese vs Normalweight	Both SERM and AI	Continuous	1.36 (0.91, 2.02)
Overweight vs Normalweight	Both SERM and AI	Intermittent	1.32 (0.63, 2.76)
Obese vs Normalweight	Both SERM and AI	Intermittent	1.66 (0.78, 3.53)
Overweight vs Normalweight	AI only	Continuous	1.1 (0.74, 1.62)
Obese vs Normalweight	AI only	Continuous	1.38 (0.92, 2.08)
Overweight vs Normalweight	AI only	Intermittent	1.13 (0.75, 1.71)
Obese vs Normalweight	AI only	Intermittent	1.43 (0.94, 2.18)

p-value for non-linearity of Age: <0.0001

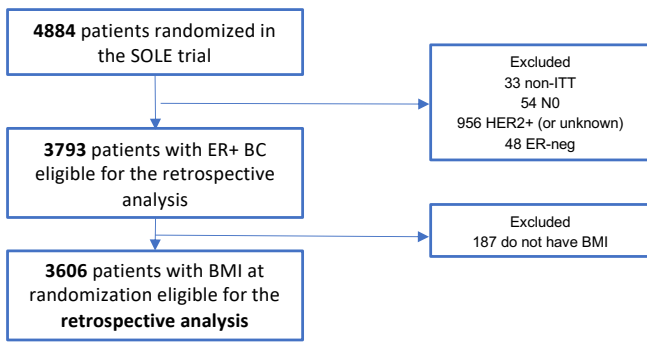
continuous BMI

p-value for non-linearity of Age: <0.0001

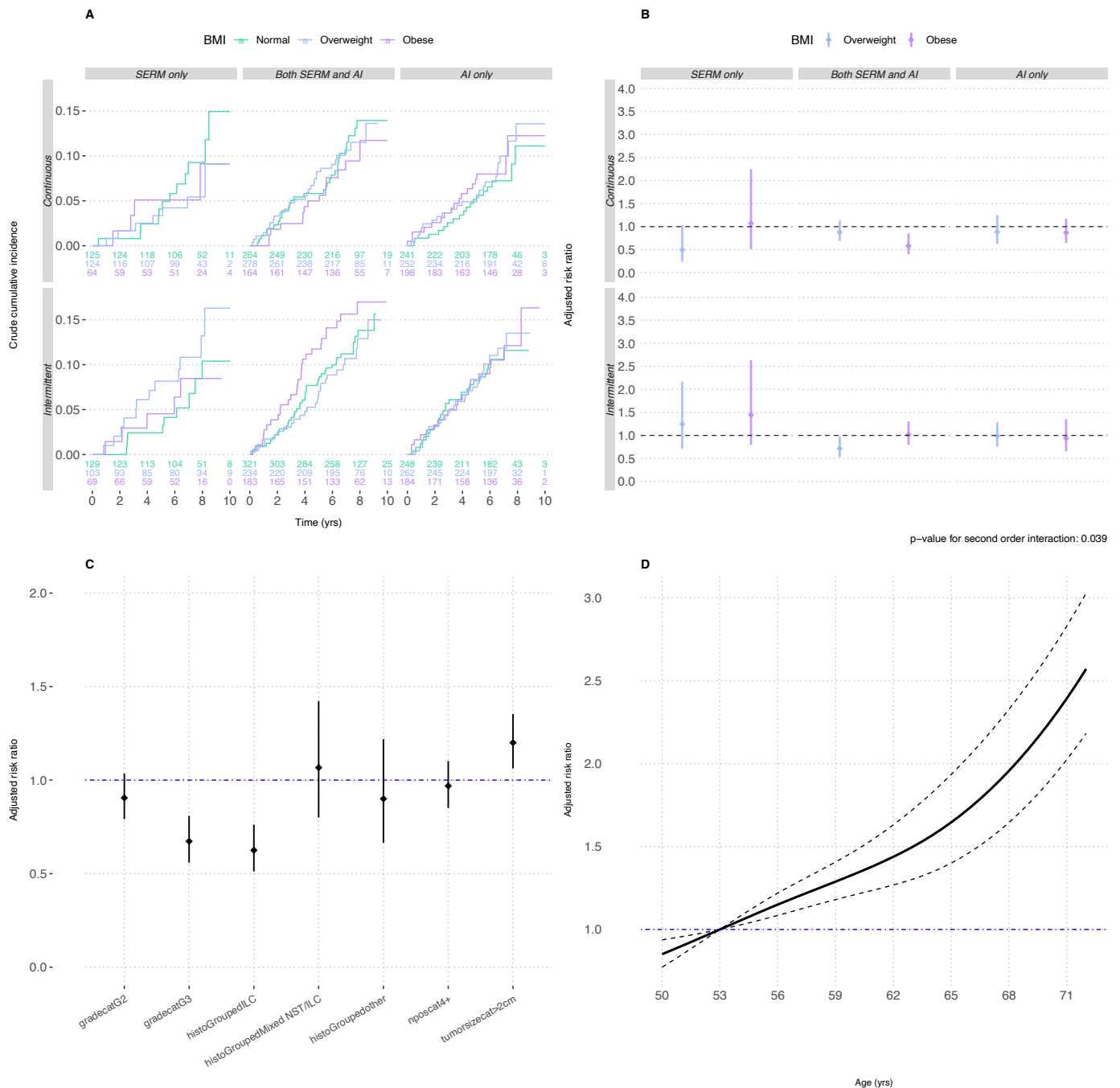
p-value for non-linearity of BMI: 7e-04

Supplementary Figures

Supplementary Figure 1: Patient flowchart

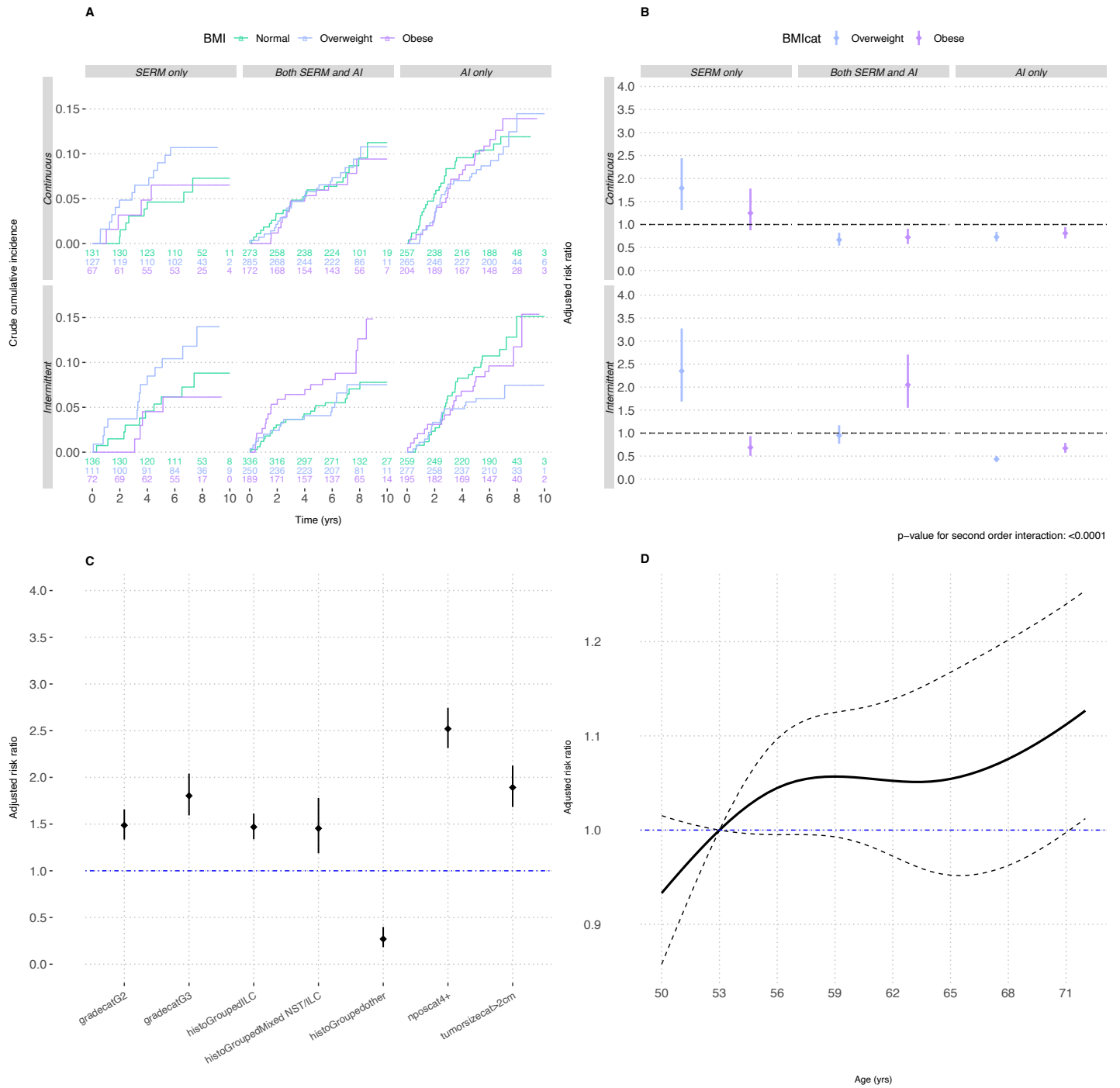


Supplementary Figure 2: DRFI – Prognostic association of categorical BMI with the competing events

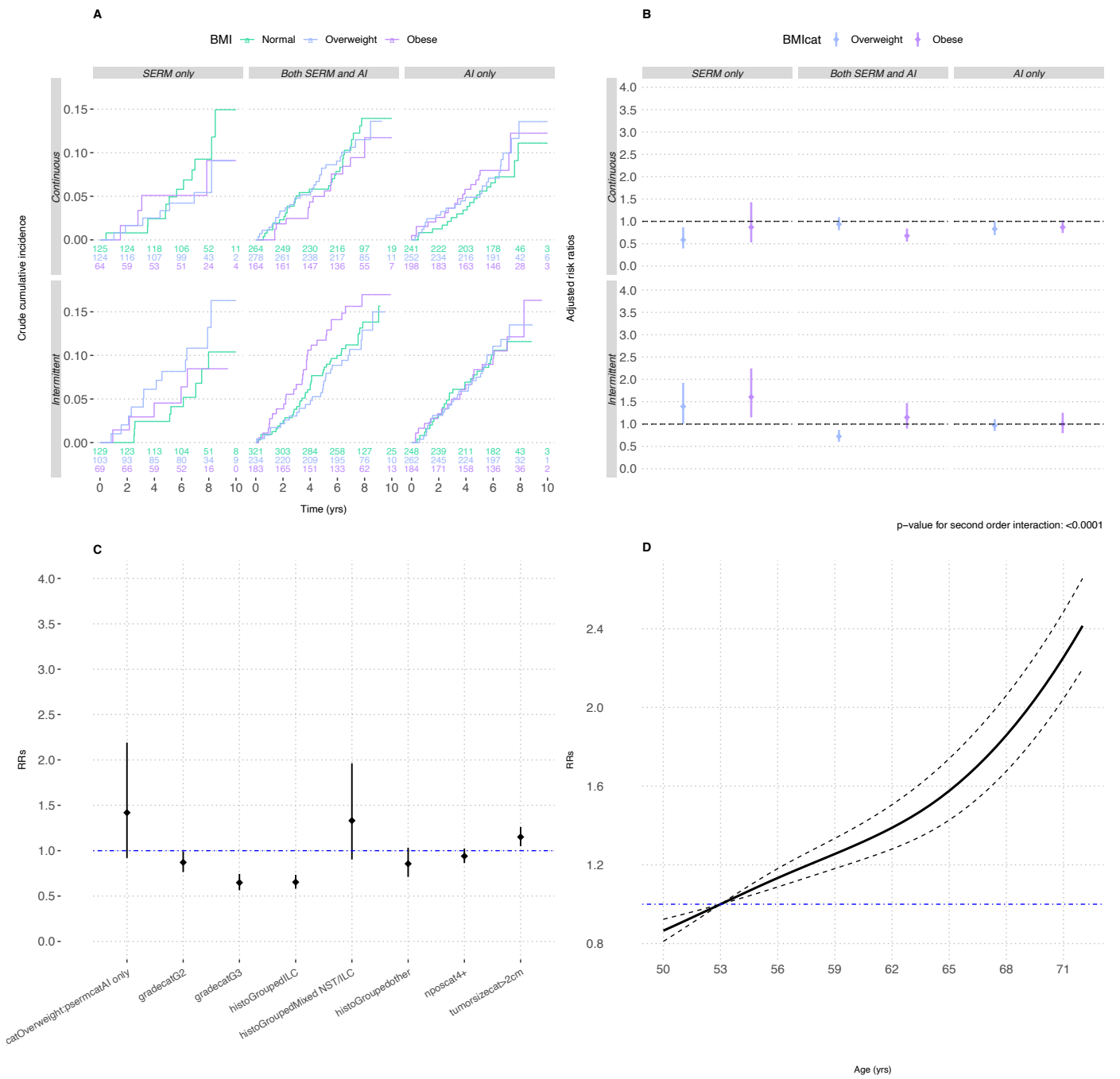


(A) Unadjusted non-parametrically estimates of CCI of the pooled events that compete with DM conditioned on prior endocrine treatment, treatment arms, and BMI category. **(B)** Forest plot of the estimated RRs of pooled competing events occurrence between Normal weight and Overweight subjects (blue) and between Normal weight and Obese subjects (purple) adjusted for tumor size, tumor grade, histology, number of positive lymph nodes, and age. Normal weight subjects are the reference category. **(C)** Estimated RRs for the other covariates in the multivariable model: tumor grade, tumor size, histology and number of positive lymph nodes. **(D)** Plot of the non-linear effect of age, modelled with a restricted cubic spline. The RRs (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95% CIs.

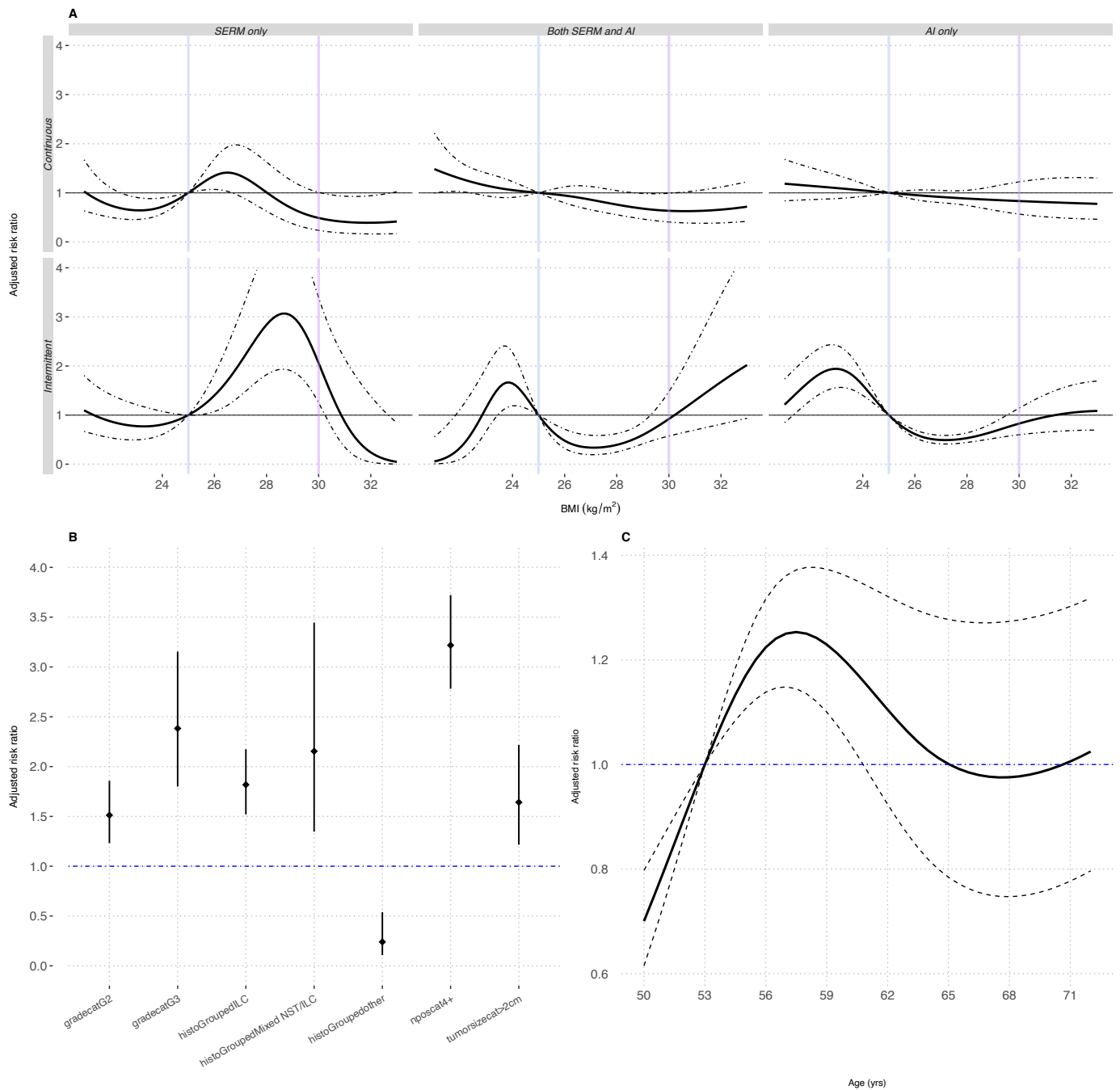
Supplementary Figure 3: DRFI – Prognostic association of categorical BMI on the main event (exploratory model with duration prior AI)



Supplementary Figure 4: DRFI – Prognostic association of categorical BMI on the competing event (exploratory model with duration prior AI)

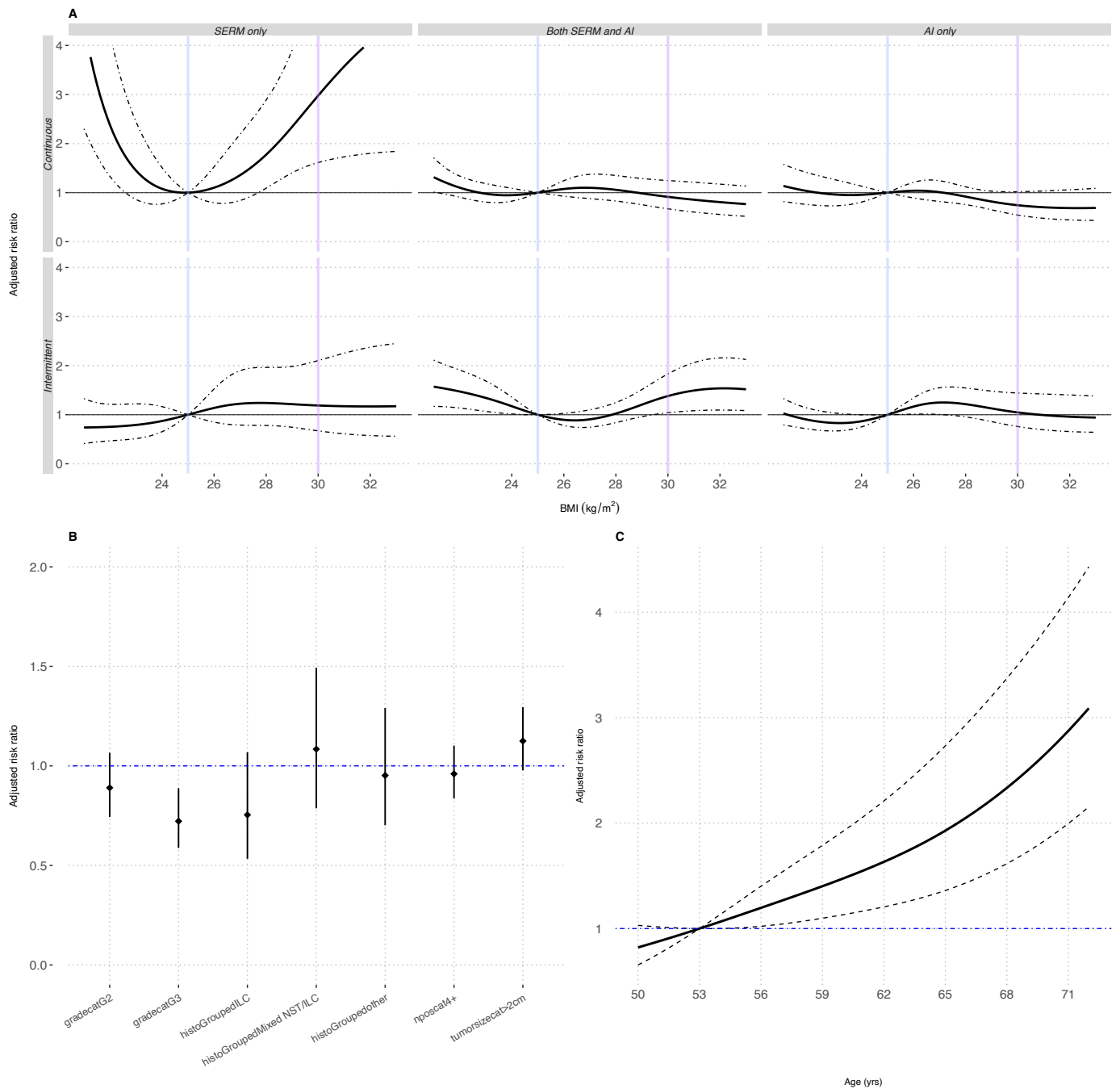


Supplementary Figure 5: DRFI – Prognostic association of continuous BMI on the main event



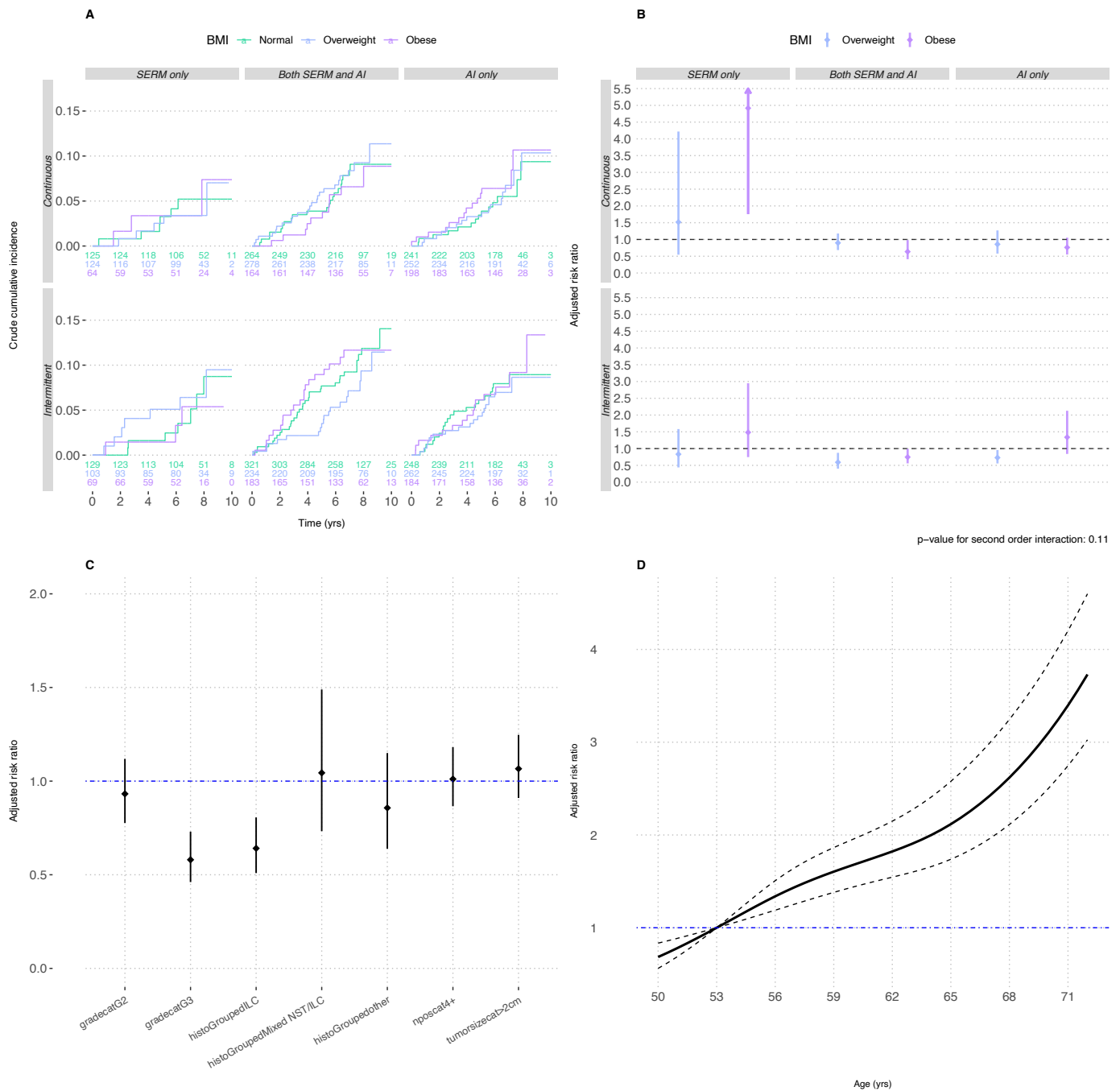
These results are based on a multivariable model in which BMI was considered as continuous variables and modelled by a restricted cubic spline. **(A)** A plot is shown for the non-linear effect of the BMI on the risk of late distant recurrences in terms of RRs adjusted for tumor size, tumor grade, histology, number of positive lymph-nodes, and age. RRs are estimated conditioned on prior endocrine treatment and treatment arm. Here a BMI of 25 Kg/m² is considered as the reference values. **(B)** The estimated risk ratios (RRs) of the adjusting tumor size, tumor grade, histology, number of positive lymph-nodes from the multivariable model on late distant recurrences. **(C)** Plot of the non-linear effect of age, modelled with a restricted cubic spline. The RRs (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95% CIs.

Supplementary Figure 6: DRFI – Prognostic association of continuous BMI with the competing events



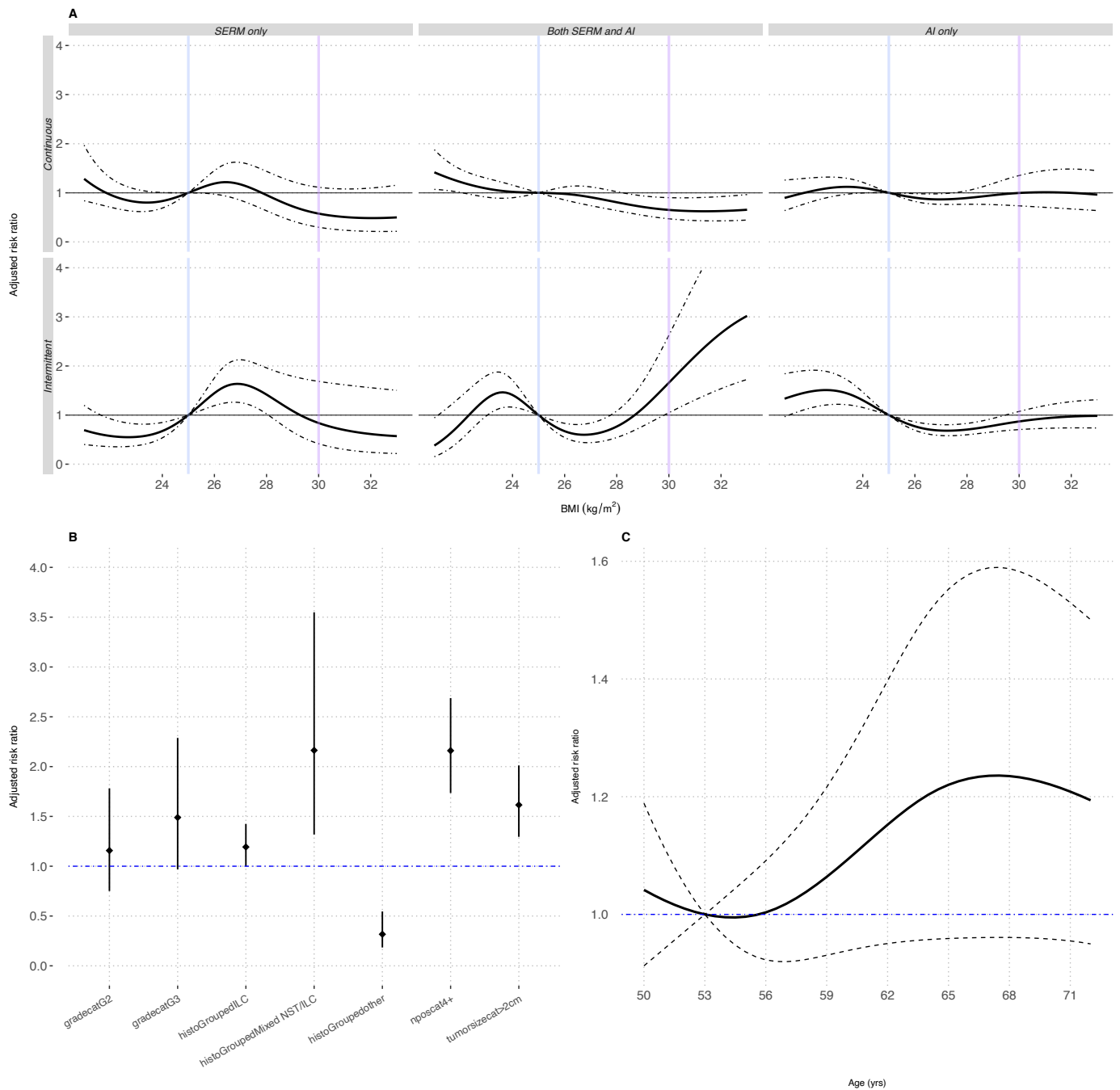
(A) A plot is shown for the non-linear effect of the BMI on the competing events in terms of RRs adjusted for tumor size, tumor grade, histology, number of positive lymph-nodes, and age. RRs are estimated conditioned on prior endocrine treatment and treatment arm. Here a BMI of 25 Kg/m² is considered as the reference values. **(B)** The estimated RR of the adjusting covariates tumor grade, tumor size, histology and number of positive lymph-nodes from the multivariable model on competing events. **(C)** Plot of the non-linear effect of age, modelled with a restricted cubic spline. The RRs (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95% CIs.

Supplementary Figure 7: BCFI – Prognostic association of categorical BMI with the competing events



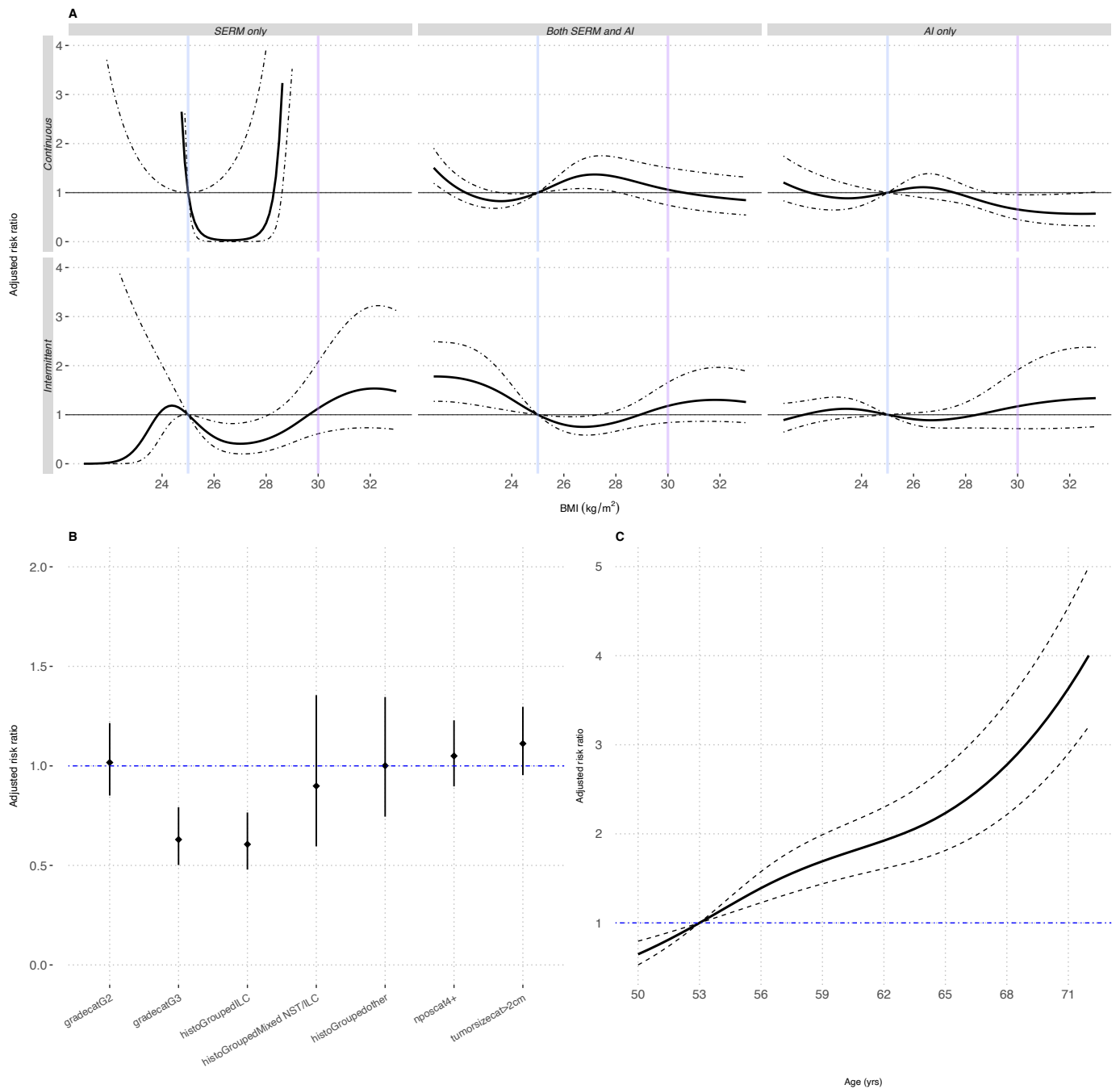
(A) Unadjusted non-parametrically estimates of CCI of the pooled events that compete with BC recurrences conditioned on prior endocrine treatment, treatment arm and BMI category. **(B)** Forest plot of the estimated RRs of pooled competing events occurrences between Normal weight and Overweight subjects (blue) and between Normal weight and Obese subjects (purple) adjusted for tumor size, tumor grade, histology, number of positive lymph nodes, and age. Normal weight subjects are the reference category. **(C)** Estimated RR for the other covariates in the multivariable model: for tumor size, tumor grade, histology, number of positive lymph nodes. **(D)** Plot of the non-linear effect of age, modelled with a restricted cubic spline. The RRs (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95% CIs.

Supplementary Figure 8: BCFI – Prognostic association of continuous BMI with the main event



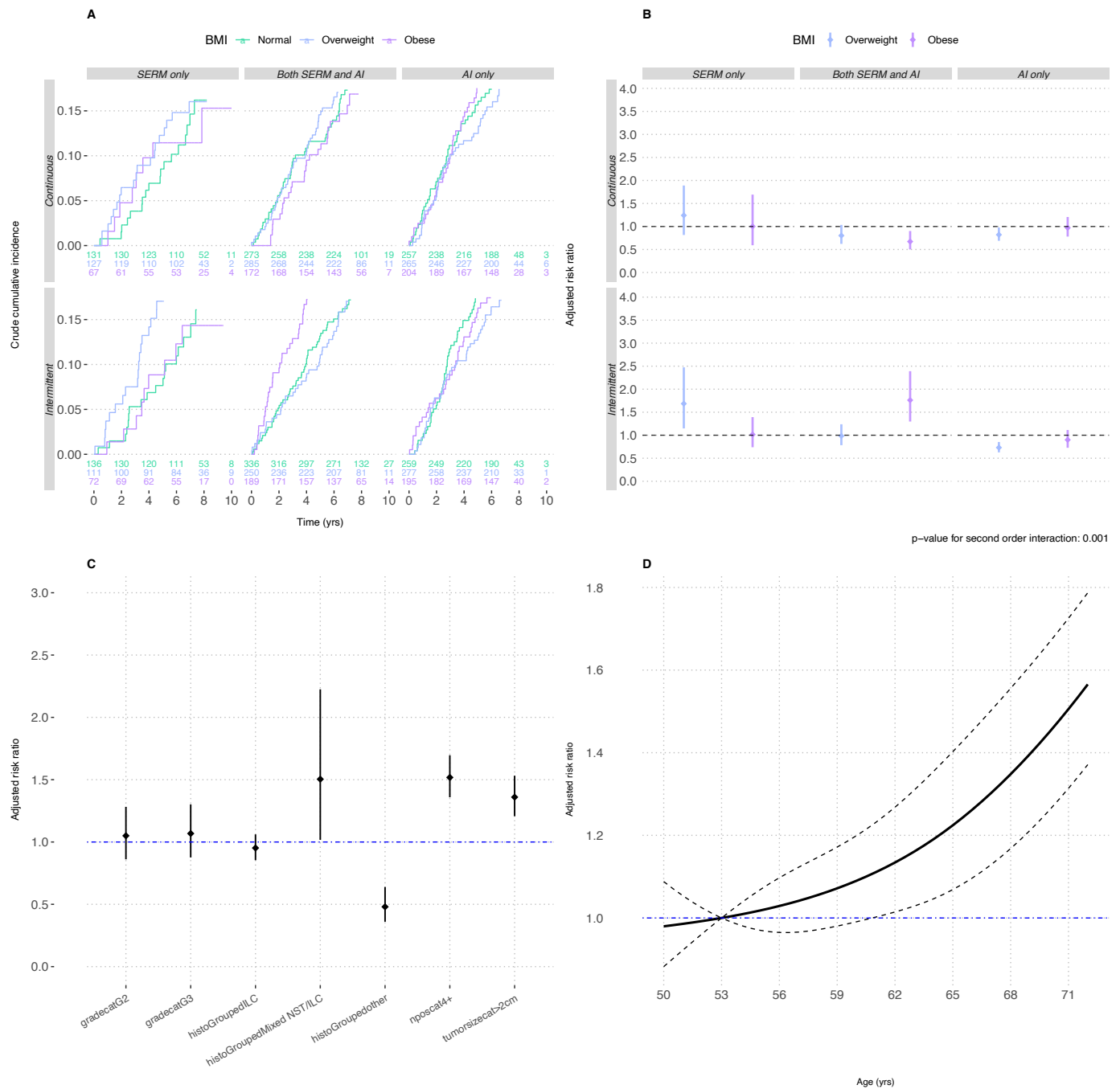
These results are based on a multivariable model in which BMI was considered as continuous variables, and modelled by a restricted cubic spline. **(A)** A plot is shown for the non-linear effect of the BMI on the risk of BC recurrences in terms of RRs adjusted for tumor size, tumor grade, histology, number of positive lymph-nodes, and age. RRs are estimated conditioned on prior endocrine treatment and treatment arm. Here a BMI of 25 Kg/m² is considered as the reference values. **(B)** The estimated risk ratios (RRs) of the adjusting covariates tumor size, tumor grade, histology, number of positive lymph-nodes from the multivariable model on BC recurrences. **(C)** Plot of the non-linear effect of age, modelled with a restricted cubic spline. The RRs (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95% CIs.

Supplementary Figure 9: BCFI – Prognostic association of continuous BMI with the competing events



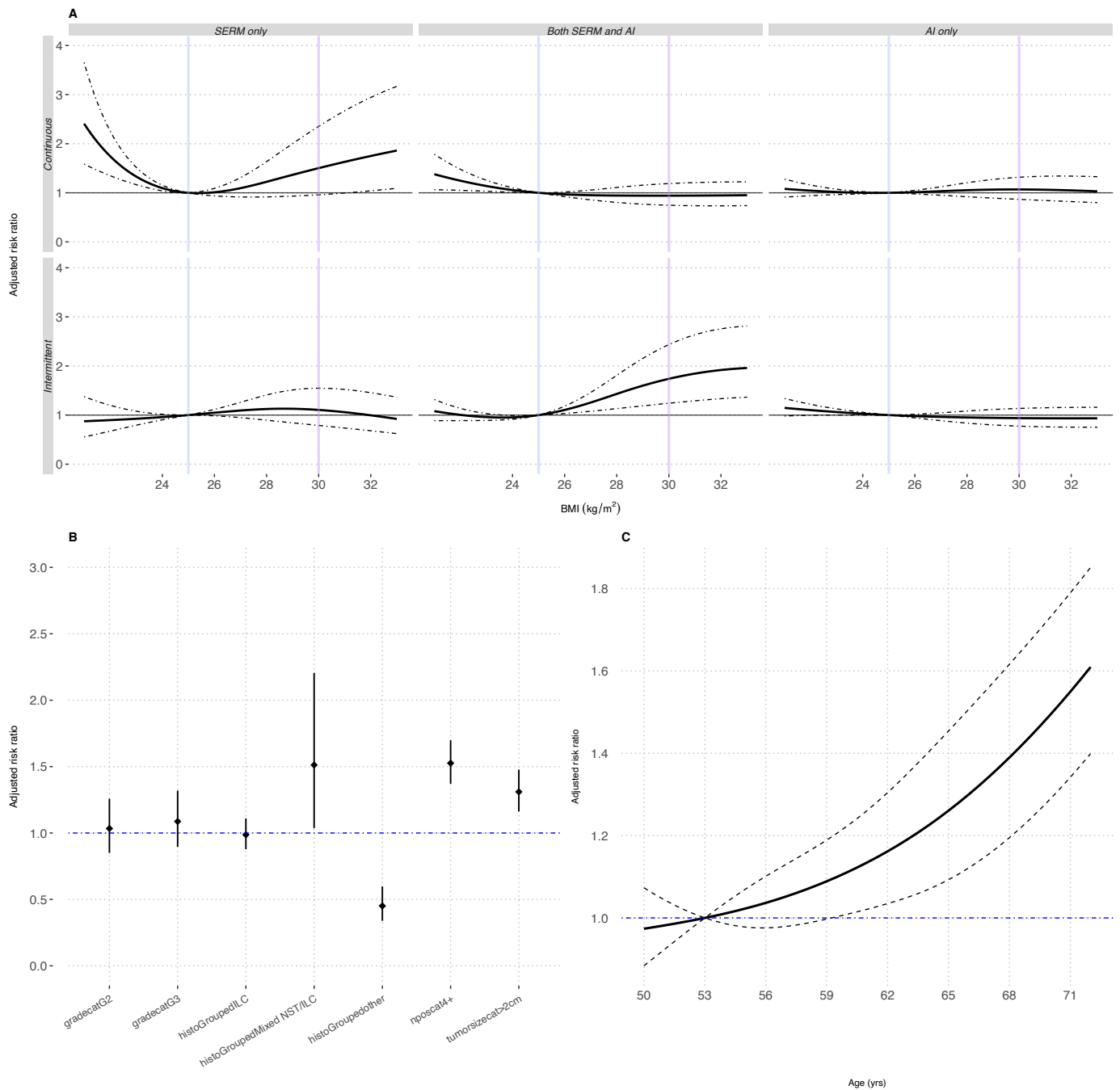
(A) A plot is shown for the non-linear effect of the BMI on the competing events in terms of RRs adjusted for tumor size, tumor grade, histology, number of positive lymph-nodes, and age. RRs are estimated conditioned on prior endocrine treatment and treatment arm. Here a BMI of 25 Kg/m² is considered as the reference values. **(B)** The estimated RRs of the adjusting covariates tumor grade, tumor size, histology and number of positive lymph-nodes from the multivariable model on competing events. **(C)** Plot of the non-linear effect of age, modelled with a restricted cubic spline. The RRs (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95% CIs.

Supplementary Figure 10: DFS – Prognostic association of categorical BMI with DFS



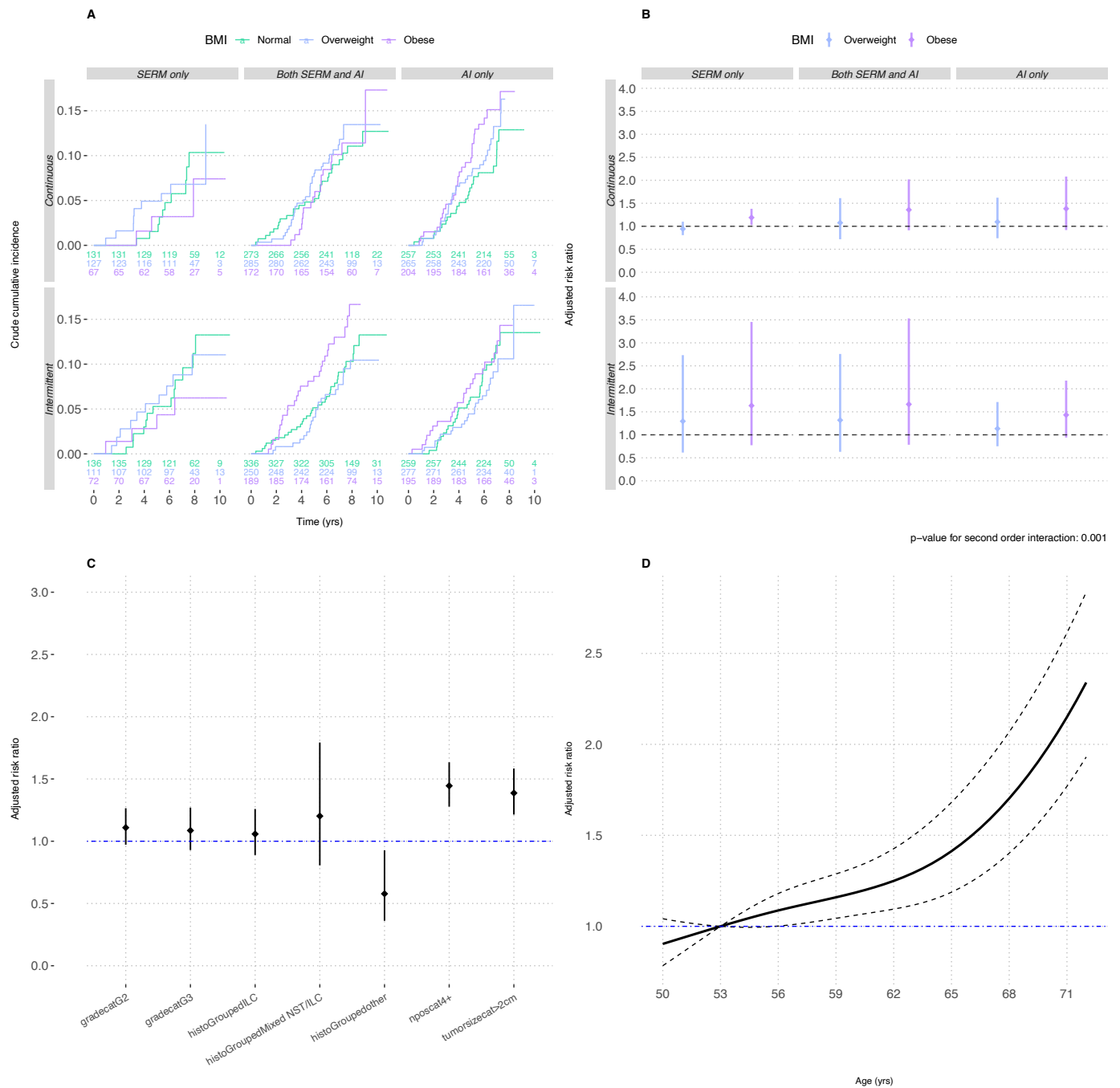
(A) Unadjusted non-parametrically estimates of CCI conditioned on prior endocrine treatment, treatment arm and BMI category. **(B)** Forest plot of the estimated RRs between Normal weight and Overweight subjects (blue) and between Normal weight and Obese subjects (purple) adjusted for tumor size, tumor grade, histology, number of positive lymph nodes, and age. Normal weight subjects are the reference category. **(C)** Estimated RRs for the other covariates in the multivariable model: tumor grade, tumor size, histology and number of positive lymph nodes. **(D)** Plot of the non-linear effect of age, modelled with a restricted cubic spline. The RRs (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95% CIs.

Supplementary Figure 11: DFS - Prognostic association of continuous BMI with DFS



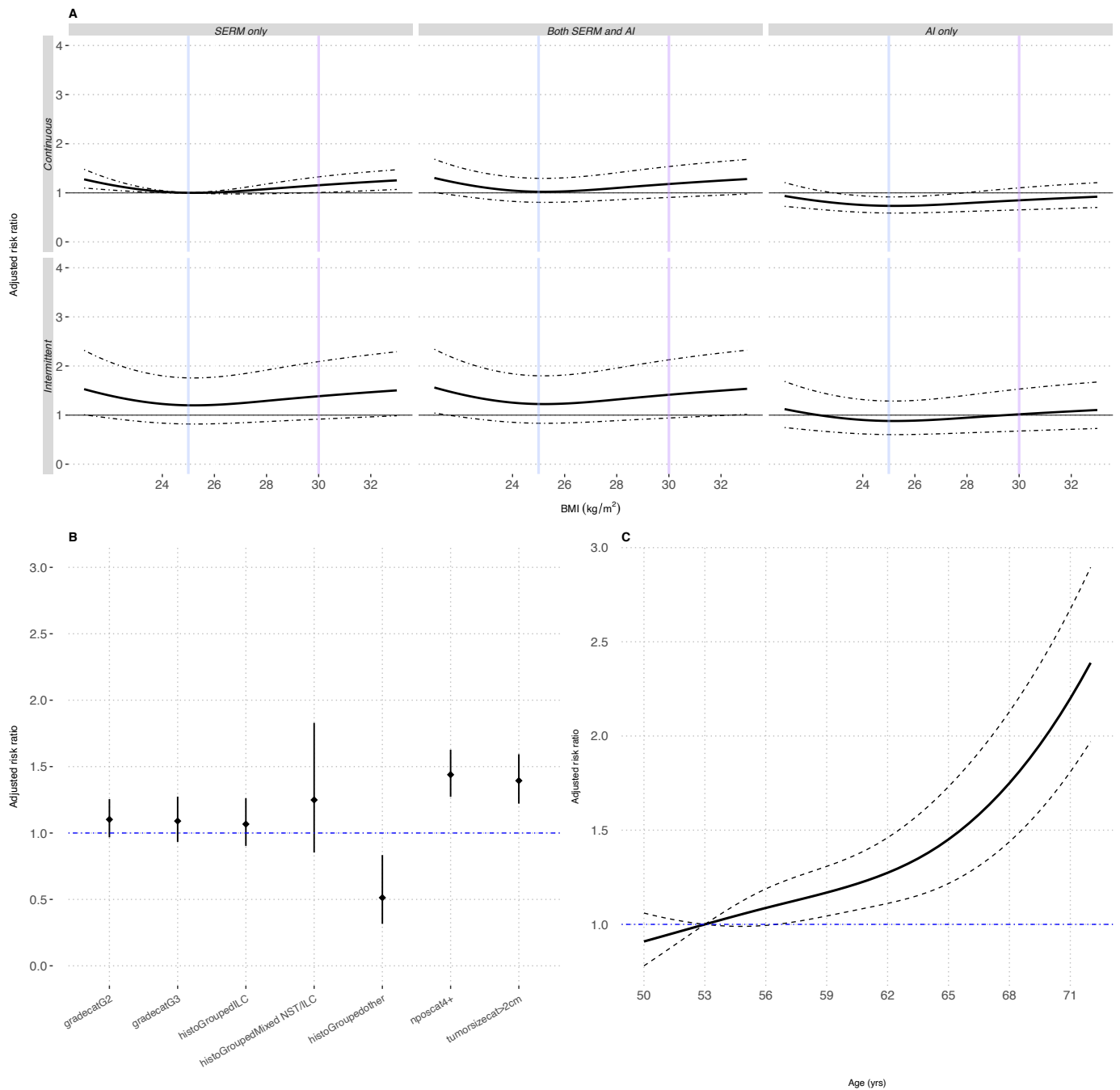
(A) A plot is shown for the non-linear effect of the BMI in terms of RRs adjusted for tumor size, tumor grade, histology, number of positive lymph-nodes, and age. RRs are estimated conditioned on prior endocrine treatment and treatment arm. Here a BMI of 25 Kg/m² is considered as the reference value. **(B)** The estimated RRs of the adjusting covariates tumor grade, tumor size, histology and number of positive lymph-nodes. **(C)** Plot of the non-linear effect of age, modelled with a restricted cubic spline. The RRs (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95% CIs.

Supplementary Figure 12: OS – Prognostic association of categorical BMI with OS



(A) Unadjusted non-parametrically estimates of CCI conditioned on prior endocrine treatment, treatment arm and BMI category. **(B)** Forest plot of the estimated RRs between Normal weight and Overweight subjects (blue) and between Normal weight and Obese subjects (purple) adjusted for tumor size, grade, histology, number of positive lymph nodes, and age. Normal weight subjects are the reference category. **(C)** Estimated RRs for the other covariates in the multivariable model: tumor grade, tumor size, histology and number of positive lymph nodes. **(D)** Plot of the non-linear effect of age, modelled with a restricted cubic spline. The RRs (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95% CIs.

Supplementary Figure 13: OS – Prognostic association of continuous BMI with OS



(A) A plot is shown for the non-linear effect of the BMI in terms of RRs adjusted for tumor size, tumor grade, histology, number of positive lymph-nodes, and age. RRs are estimated conditioned on prior endocrine treatment and treatment arm. Here a BMI of 25 Kg/m² is considered as the reference value. **(B)** The estimated risk ratios (RRs) of the adjusting covariates tumor grade, tumor size, histology and number of positive lymph-nodes. **(C)** Plot of the non-linear effect of age, modelled with a restricted cubic spline. The RRs (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95% CIs.